Claim 1:	Dixon
	same molecular structure . . . ." (*Id.*, 1575).[18]

As a result, Dixon anticipates claim 1 of the '338 patent.

2. Dependent claims 3 and 4 are anticipated by Dixon.

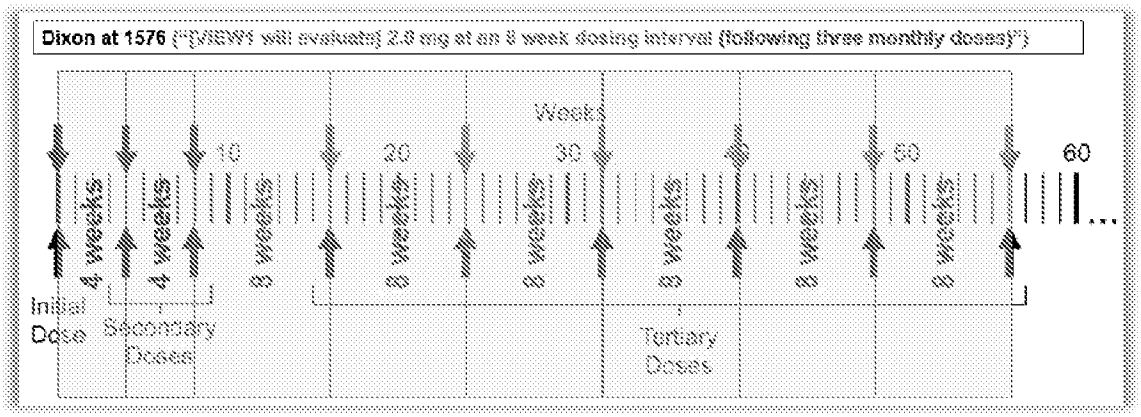
129. I have been informed that claims 3 and 4 can be described as "dependent" on claim 1. It is my understanding that a dependent claim incorporates the elements of the claims from which it depends.

130. Claim 3 limits the method of claim 1 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." And, claim 4 further limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

131. As illustrated in my modified Figure 1 of the '338 patent as provided below, which exemplifies a regimen falling within the scope of all the challenged claims, Dixon discloses the elements of claim 3 (each secondary dose is

[18] As discussed above, the structure and sequence of VEGF Trap-Eye/aflibercept was well known to those of ordinary skill in the art. (*See, e.g.*, *supra* Sec. VIII(A)).

administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

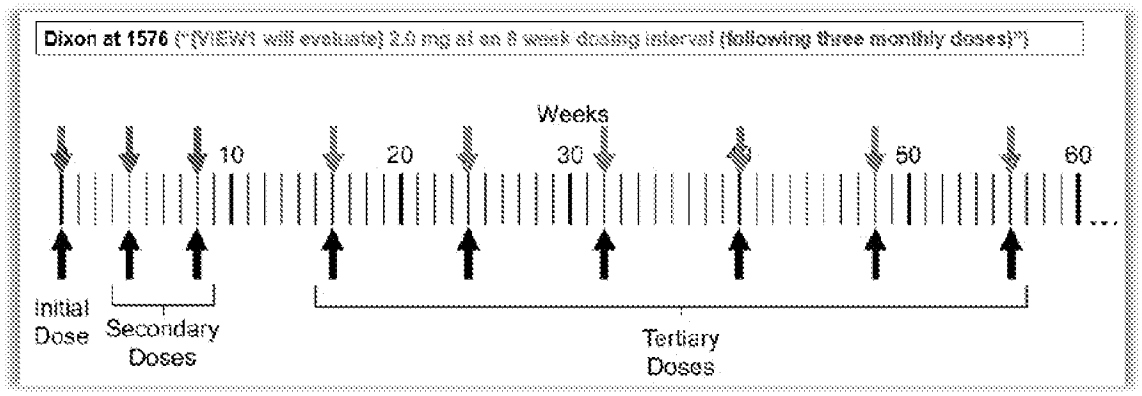
132. Accordingly, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Dixon.

3. Dependent claim 5 is anticipated by Dixon.

133. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

134. Dixon discloses that the every-8-week aspect of the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing [T]he primary

outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)). As illustrated in my modified Figure 1 below, the "8 week dosing interval" disclosed in Dixon would result in "at least 5 tertiary doses," e.g., administered at weeks 16, 24, 32, 40, and 48 (red arrows), each administered 8 weeks after the immediately preceding dose:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

135. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Dixon.

4. Dependent claims 6 and 7 are anticipated by Dixon.

136. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

137. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD, which is an angiogenic eye disorder. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Thus, Dixon discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

138. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the '338 patent are anticipated by Dixon.

5. Dependent claims 8-10 are anticipated by Dixon.

139. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

140. Claim 9 depends from claim 8 and specifies intraocular administration.

141. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

142. Dixon discloses that the VIEW1 and VIEW2 studies "will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye." (Ex.1006, Dixon, 1576 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Dixon.

143. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 8-10 are anticipated by Dixon.

6. Dependent claims 11 and 13 are anticipated by Dixon.

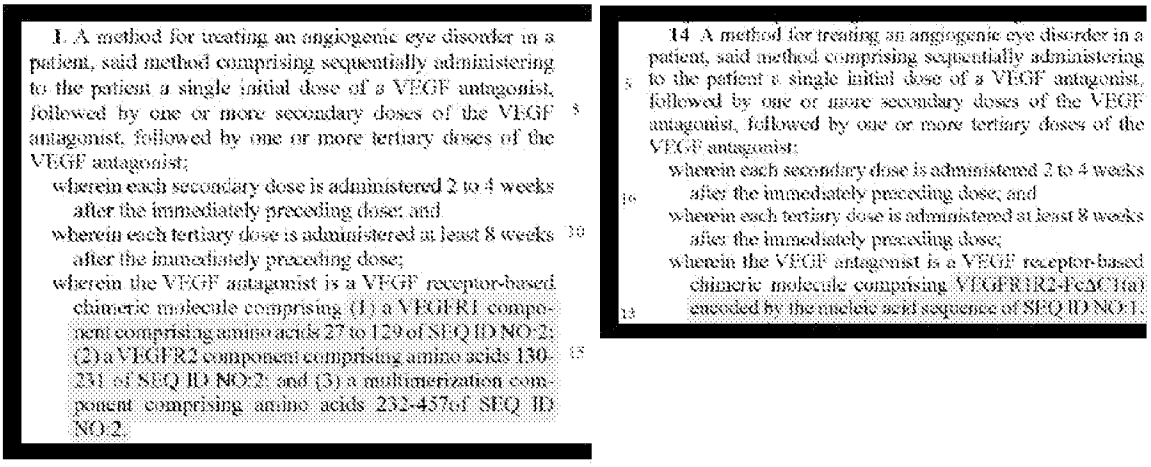
144. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

145. Dixon discloses the treatment arms in the VIEW1 and VIEW2 studies which included "intravitreal VEGF Trap-Eye at…2.0 mg at an 8 week dosing interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 11 and 13.

146. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Dixon.

7. Independent claim 14 is anticipated by Dixon.

147. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause:



1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

14. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

148. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶ 128), it is also my opinion that Dixon discloses these identical elements in claim 14.

149. Second, in my opinion, Dixon also discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-

C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

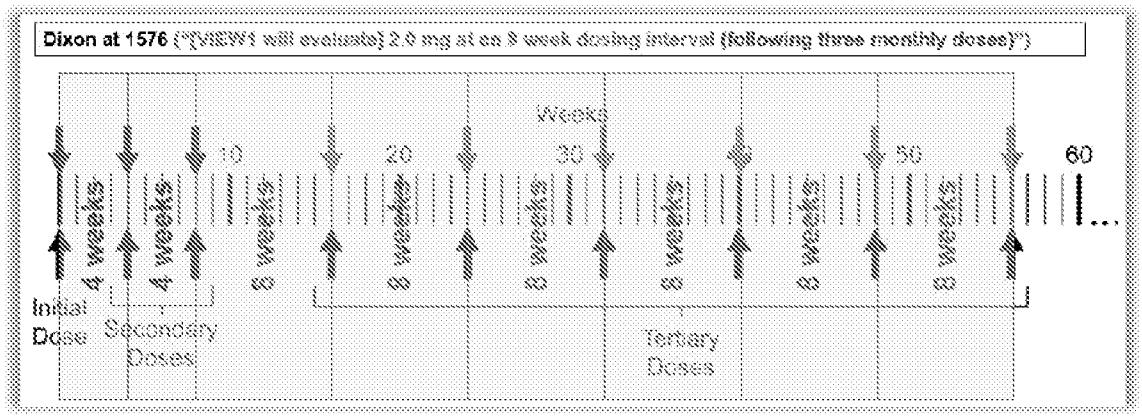
150. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Dixon.

8. Dependent claims 16 and 17 are anticipated by Dixon.

151. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

152. As I explained with respect to claims 3 and 4 above, Dixon discloses the elements of claim 16 (each secondary dose administered 4 weeks after the

immediately preceding dose) and claim 17 (each tertiary dose is administered 8 weeks after the immediately preceding dose), as is illustrated in modified Figure 1 below:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

153. Accordingly, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Dixon.

9. Dependent claims 18 and 20 are anticipated by Dixon.

154. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

155. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Dixon therefore expressly discloses treating an angiogenic eye disorder, including AMD, as required by claims 18 and 20.

156. Thus, for these reasons, as well as for the reasons discussed above for claims 14, 16, and 17, it is my opinion that claims 18 and 20 of the '338 patent are anticipated by Dixon.

10. Dependent claim 19 is anticipated by Dixon.

157. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

158. Dixon discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)).

159. As explained above with respect to claim 5, moreover, one year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses (red arrows in above figure). For example, after three monthly doses at weeks 0, 4, and 8, the every-8-week dosing regimen disclosed in Dixon for the VIEW1 and VIEW2 studies would result in doses being administered at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered at least 8 weeks after the immediately preceding dose, before the end of the one year trial.

160. Thus, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claim 19 of the '338 patent is anticipated by Dixon.

11. Dependent claims 21-23 are anticipated by Dixon.

161. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

162. Claim 22 depends from claim 21 and specifies intraocular administration.

163. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

164. To a person of ordinary skill in the art, it is well understood that intravitreal administration is a form of intraocular administration. Intraocular administration refers to administration to the eye generally, while intravitreal administration, a subset of intraocular administration, refers to administration directly into the vitreous of the eye.

165. In Dixon's disclosure of the VIEW1 and VIEW2 studies, Dixon stated that the study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses intravitreal administration.

166. Therefore, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 21-23 are anticipated by Dixon.

12. Dependent claims 24 and 26 are anticipated by Dixon.

167. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

168. Dixon discloses the VIEW1 and VIEW2 studies in which the treatment arms included "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8 week dosing

interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 24 and 26.

169. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Dixon.

B. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by Adis (Ex.1007).

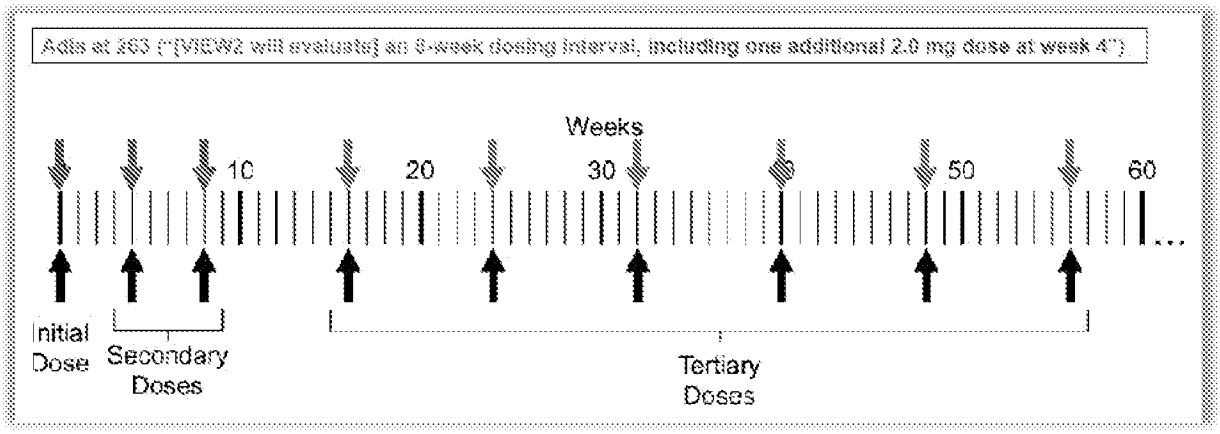
1. Claim 1 of the '338 patent is anticipated by Adis.

170. Claim 1 of the '338 patent has been set forth above.

171. I was asked to review the challenged claims of the '338 patent and compare them to the disclosures of Adis. It is my opinion that Adis discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

172. For example, like Dixon above, Adis discloses Regeneron's planned Phase 3 trials being conducted with VEGF Trap-Eye, VIEW1 and VIEW2. Adis discloses the VIEW regimen, i.e., "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Ex.1007, Adis, 263). In other words, one of the dosing regimens being tested in the VIEW trials was every-8-week dosing following three monthly doses. This has been shown using the same overlay presented above, in which I have used Figure 1 of the '338 patent, which shows a

regimen that exemplifies each challenged claim, to illustrate how Adis discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

173. While Adis does not use the exact terms "initial," "secondary," and "tertiary," one of ordinary skill in the art readily would have recognized that the "initial dose" would have been the first dose given—in this case the dose given at time zero—and that the "secondary doses . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose," could be found in Adis' disclosure of "an 8-week dosing interval, *including one additional 2.0 mg dose at week 4*" (blue arrows). (*See, e.g.*, Ex.1007, Adis, 263 (emphasis added)).

174. Similarly, one of ordinary skill in the art would have recognized that the "tertiary doses . . . wherein each tertiary dose is administered at least 8 weeks

after the immediately preceding dose," correspond to the "8-week dosing interval" doses disclosed in Adis (red arrows). (*See, e.g., id.*).

175. In my opinion, the VIEW dosing regimen described in Adis is the precise dosing regimen that was described in Figure 1 in the '338 patent and which falls squarely within the scope of claim 1.

176. With respect to the VEGF antagonist element of claim 1, I note that this description is merely a recitation of the molecular architecture of the "aflibercept" and "VEGF Trap-Eye" disclosed in Adis, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the

same drug); Ex.1093). As a result, through Adis' disclosure of VEGF Trap-Eye/aflibercept, Adis discloses this aspect of claim 1.[19]

177. Accordingly, for these reasons, it is my opinion that claim 1 of the '338 patent is anticipated by Adis.

2. Dependent claims 3 and 4 are anticipated by Adis.

178. Dependent claim 3 claims the method of claim 1, "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

179. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

180. As discussed above and illustrated in my modified Figure 1 of the '338 patent, Adis discloses the elements of claim 3 (each secondary dose administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):

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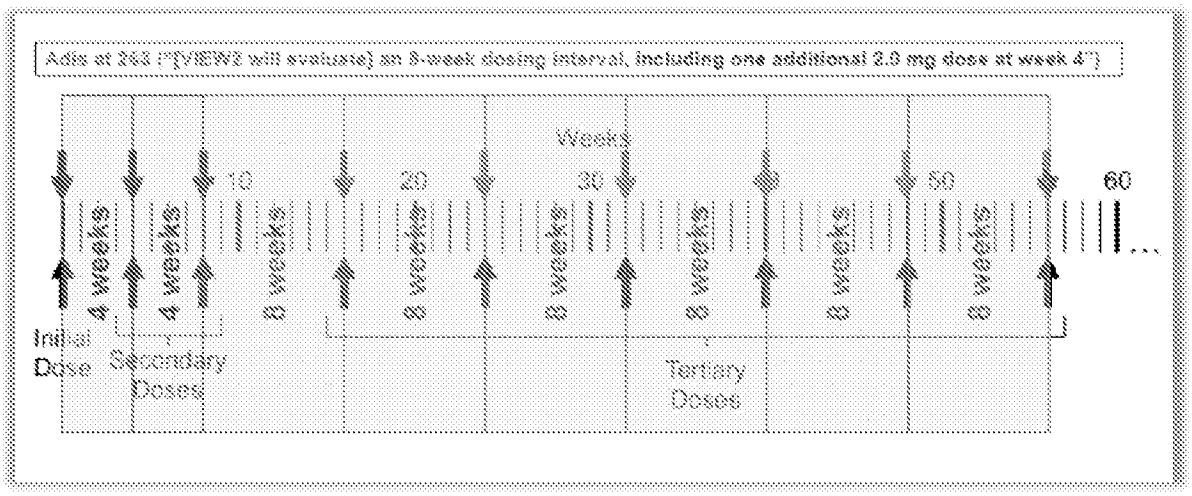
[19] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1007, Adis, 268 ("After the last fixed-dose administration at week 12, patients from all dose groups required on average only one additional injection over the following 20 weeks to maintain visual acuity gain achieved.").



(Ex.1001, '338 patent, Fig.1 (modifications added)).

181. Accordingly, for these reasons, as well as the reasons presented for claim 1, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Adis.

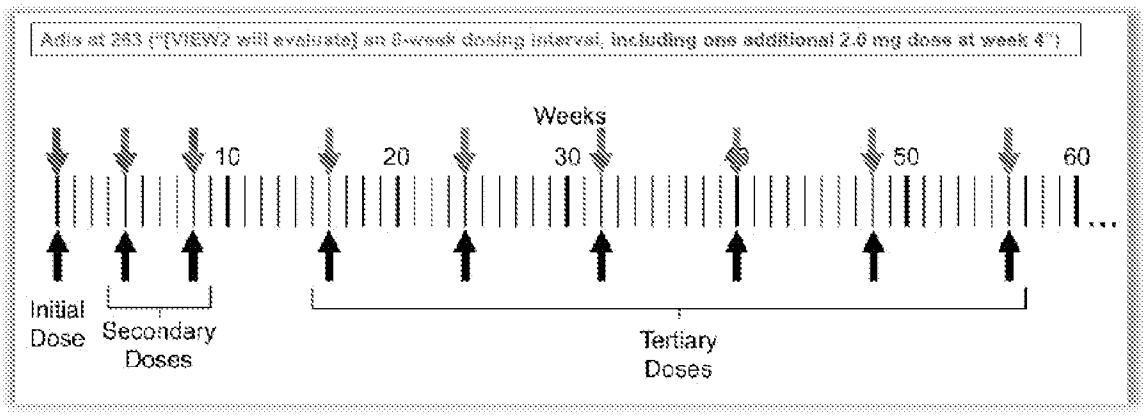
3. Dependent claim 5 is anticipated by Adis.

182. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

183. Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1007, Adis, 263 ("Patients will continue to be treated and followed for an additional year, ***after the first year of treatment***" and "[t]he primary endpoint

will be the proportion of patients treated with aflibercept who maintain vision ***at the end of 1 year*** compared with ranibizumab patients." (emphases added)).

184. One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses administered at least 8 weeks after the immediately preceding dose. Again, a graphic is useful in illustrating this:



(Ex.1001, '338 patent, Fig.1 (modifications added)). Using the modified graphic from the '338 patent, it is apparent that the every-8-week dosing regimen disclosed in Adis for the VIEW1 and VIEW2 studies would result in "tertiary" doses being administered at least at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered before the end of the one-year trial.

185. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Adis.

4. Dependent claims 6 and 7 are anticipated by Adis.

186. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

187. The Adis reference indicates in the abstract that aflibercept was being developed for eye disorders and that "[b]lockade of VEGF can also prevent blood vessel formation and vasuclar [sic] leakage associated with wet age-related macular degeneration (AMD)." (Ex.1007, Adis, 261). Likewise, Adis discusses Regeneron's disclosures of the VIEW1 and VIEW2 trials, which were intended to study VEGF Trap-Eye/aflibercept in wet AMD. (*Id.*, 263). It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD, which is an angiogenic eye disorder, that the dosing regimen of doses at weeks 0, 4, and 8, followed by every-8-week dosing, was disclosed. Thus, Adis discloses the treatment of AMD, a well-known angiogenic eye disorder.

188. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the '338 patent are anticipated by Adis.

5. Dependent claims 8-10 are anticipated by Adis.

189. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

190. Claim 9 depends from claim 8 and specifies intraocular administration.

191. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

192. In Adis' disclosure of the VIEW studies, Adis states that the study "will evaluate the safety and efficacy of intravitreal aflibercept." (Ex.1007, Adis, 263). Adis also notes that Regeneron's Phase 2 trial was designed to "evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens." (*Id.*). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Adis.

193. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 of the '338 patent are anticipated by Adis.

6. Dependent claims 11 and 13 are anticipated by Adis.

194. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the

VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

195. Adis discloses the VIEW1 and VIEW2 studies in which the treatment arms included VEGF Trap-Eye/aflibercept administered at a 2.0 mg dose. (Ex.1007, Adis, 263). Adis therefore expressly discloses the doses of claims 11 and 13.

196. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Adis.

7. Independent claim 14 is anticipated by Adis.

197. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

198. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 170-77), it is also my opinion that Adis discloses these identical elements in claim 14.

199. Second, in my opinion, Adis discloses the VEGF antagonist element of claim 14. Adis expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide

sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

200. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Adis.

8. Dependent claims 16 and 17 are anticipated by Adis.

201. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

202. These elements are similar in scope to those discussed above with respect to claims 3 and 4, and as I explained with respect to those claims, Adis

discloses the elements of "each secondary dose is administered 4 weeks after the immediately preceding dose" and "each tertiary dose is administered 8 weeks after the immediately preceding dose." (*See, e.g.*, Ex.1007, Adis, 263 ("2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4.")).

203. Accordingly, for these reasons, as well as for the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Adis.

9. Dependent claims 18 and 20 are anticipated by Adis.

204. Claim 18 depends from claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 depends from claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

205. These elements are similar in scope to those discussed above with respect to claims 6 and 7, and as I explained with respect to those claims, Adis discloses the VIEW1 and VIEW2 trials, and the treatment arms used therein, which were designed to assess wet AMD. (*See, e.g.*, Ex.1007, Adis, 263 ("Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD . . . .")). Adis therefore expressly discloses treating AMD, an angiogenic eye disorder.

206. Thus, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 of the '338 patent are anticipated by Adis.

10. Dependent claim 19 is anticipated by Adis.

207. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

208. As explained above with respect to claim 5, Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (*See, e.g.*, Ex.1007, Adis, 263 ("The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision *at the end of 1 year* . . . .") (emphasis added)). One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses administered at least 8 weeks after the immediately preceding dose.

209. Thus, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 of the '338 patent is anticipated by Adis.

11. Dependent claims 21-23 are anticipated by Adis.

210. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

211. Claim 22 depends from claim 21 and specifies intraocular administration.

212. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

213. As discussed above with respect to claims 8-10, Adis discloses that the VIEW trials, and the treatment arms used therein, were assessing intravitreally-administered aflibercept. (*See, e.g.*, Ex.1007, Adis, 263 ("VIEW1 . . . will evaluate the safety and efficacy of intravitreal aflibercept . . . .")). Adis therefore expressly discloses intravitreal administration of the VEGF antagonist.

214. Therefore, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Adis.

12. Dependent claims 24 and 26 are anticipated by Adis.

215. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

216. As discussed above with respect to claims 11 and 13, Adis discloses that the VIEW1 and VIEW2 studies were intended to assess a 2.0 mg dose. (*See, e.g.*, Ex.1007, Adis, 263). Adis therefore expressly discloses a 2.0 mg doses of VEGF Trap-Eye/aflibercept.

217. Therefore, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Adis.

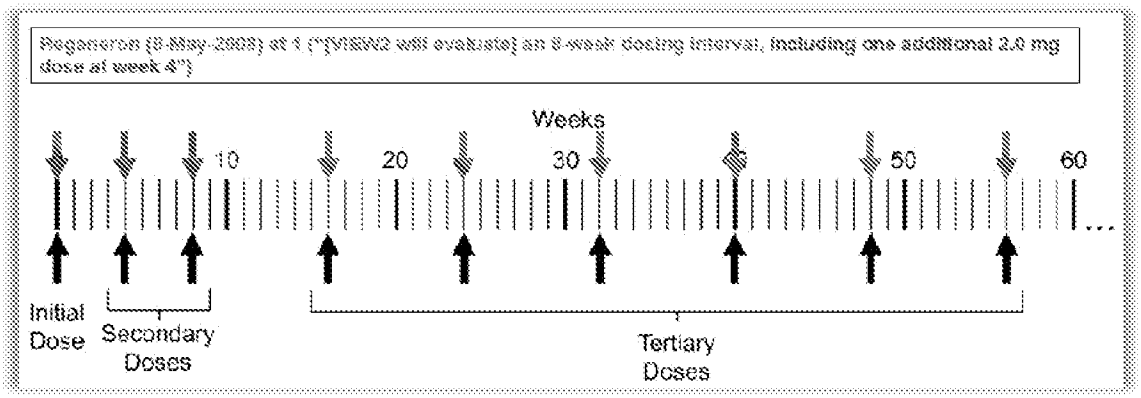
C. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by the Regeneron Press Release Dated May 8, 2008 (Regeneron (8-May-2008) (Ex.1013).

1. Independent claim 1 of the '338 patent is anticipated by Regeneron (8-May-2008).

218. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of the Regeneron Press Release, dated May 8, 2008. It is my opinion that Regeneron (8-May-2008) discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

219. For example, like Dixon and Adis above, Regeneron (8-May-2008) discloses the VIEW Phase 3 trials being conducted with VEGF Trap-Eye, and explains that VIEW2 will assess VEGF Trap-Eye at "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron

(8-May-2008), 1). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how Regeneron (8-May-2008) discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing "at an 8-week dosing interval" would result in doses at day 0 and at week 8, and when adding "one additional 2.0 mg dose at week 4," this would result in three monthly doses (blue arrows) (i.e., doses at day 0 (i.e. "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

220. Regeneron (8-May-2008) further states that "[a]fter the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12

weeks, but not more often than every 4 weeks." (Ex.1013, Regeneron (8-May-2008), 1).

221. With respect to the VEGF antagonist element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in Regeneron (8-May-2008), a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093). As a result, through Regeneron (8-May-2008)'s disclosure

of VEGF Trap-Eye/aflibercept, Regeneron (8-May-2008) discloses this aspect of claim 1. .[20]

222. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by Regeneron (8-May-2008).

2. Dependent claims 3 and 4 are anticipated by Regeneron (8-May-2008).

223. Dependent claim 3 claims the method of claim 1, "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

224. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

225. As illustrated in my modified Figure 1 of the '338 patent below, Regeneron (8-May-2008) discloses the elements of claims 3 and 4. In discussing the first year of the VIEW2 study, Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg

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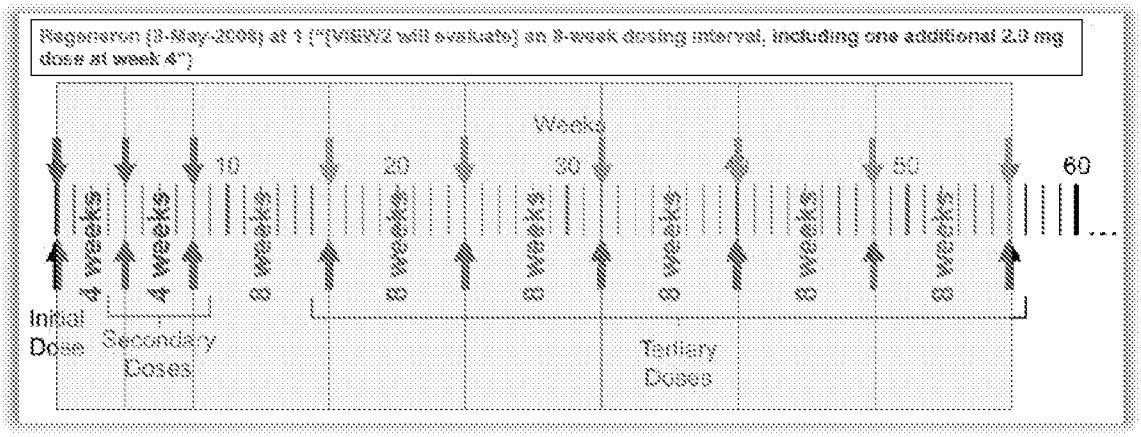
[20] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1013, Regeneron (8-May-2008), 1 ("[P]atients on the PRN dosing schedule maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12 through week 32 of the study.").

dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, and consistent with the figure below, this dosing schedule consists of a 2.0 mg dose at day 0 (i.e., an "initial dose"), 2.0 mg doses at weeks 4 and 8 (i.e., "secondary doses"), and 2.0 mg doses every 8 weeks (i.e., "tertiary doses") for the remainder of the year:



(Ex.1001, '338 patent, Fig.1 (modifications added (initial and secondary doses indicated by blue arrows and tertiary doses indicated by red arrows)).

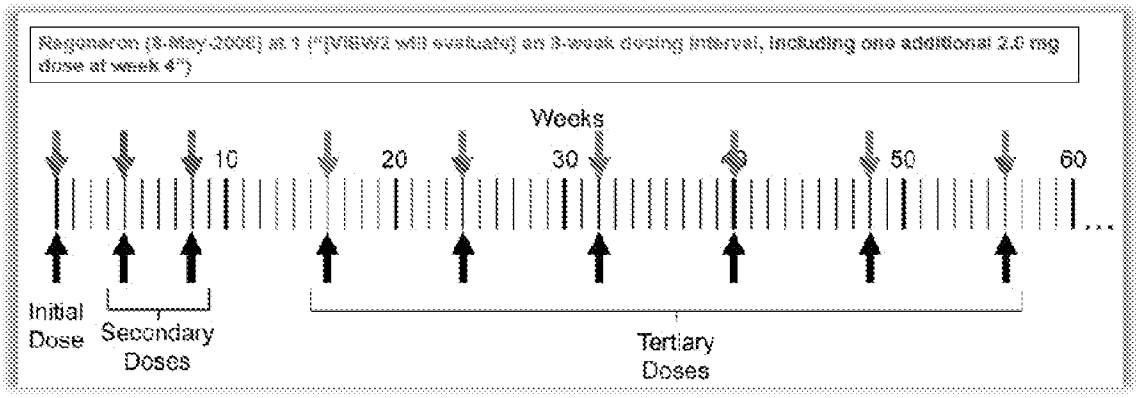
226. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by Regeneron (8-May-2008).

3. Dependent claim 5 is anticipated by Regeneron (8-May-2008).

227. For the same reasons as above for claims 3 and 4, Regeneron (8-May-2008) discloses the elements of claim 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after

the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

228. Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

229. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by Regeneron (8-May-2008).

4. Dependent claims 6 and 7 are anticipated by Regeneron (8-May-2008).

230. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

231. Claim 7 further limits the method of claim 6 to recite "wherein the angiogenic eye disorder is age related macular degeneration."

232. Regeneron (8-May-2008) expressly discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye in wet AMD, which is a well-known angiogenic eye disorder. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title).

233. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by Regeneron (8-May-2008).

5. Dependent claims 8-10 are anticipated by Regeneron (8-May-2008).

234. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

235. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

236. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

237. Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). This element is therefore expressly disclosed and taught by Regeneron (8-May-2008).

238. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by Regeneron (8-May-2008).

6. Dependent claims 11 and 13 are anticipated by Regeneron (8-May-2008).

239. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

240. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

241. Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron

(8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the doses of claims 11 and 13.

242. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by Regeneron (8-May-2008).

7. Independent claim 14 is anticipated by Regeneron (8-May-2008).

243. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

244. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 218-22), it is also my opinion that Regeneron (8-May-2008) discloses these identical elements in claim 14.

245. Second, in my opinion, Regeneron (8-May-2008) discloses the VEGF antagonist element of claim 14. Just as for claim 1, Regeneron (8-May-2008) expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced

amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

246. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Regeneron (8-May-2008).

8. Dependent claims 16 and 17 are anticipated by Regeneron (8-May-2008).

247. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

248. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

249. As discussed with respect to claims 3 and 4 above, Regeneron (8-May-2008) discloses the elements of claims 16 and 17. Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, this dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

250. For these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by Regeneron (8-May-2008).

9. Dependent claims 18 and 20 are anticipated by Regeneron (8-May-2008).

251. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

252. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

253. As discussed with claims 6 and 7 above, Regeneron (8-May-2008) discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye

in wet AMD. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title). Regeneron (8-May-2008) therefore expressly discloses treating AMD, an angiogenic eye disorder.

254. Therefore, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by Regeneron (8-May-2008).

10. Dependent claim 19 is anticipated by Regeneron (8-May-2008).

255. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

256. As discussed with claim 5, Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). An 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

257. Accordingly, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by Regeneron (8-May-2008).

11. Dependent claims 21-23 are anticipated by Regeneron (8-May-2008).

258. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

259. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

260. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

261. As discussed with claims 8-10 above, Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses intravitreal administration of the VEGF antagonist.

262. Thus, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Regeneron (8-May-2008).

12. Dependent claims 24 and 26 are anticipated by Regeneron (8-May-2008).

263. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

264. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

265. As discussed with claims 11 and 13 above, Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the claimed doses.

266. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Regeneron (8-May-2008).

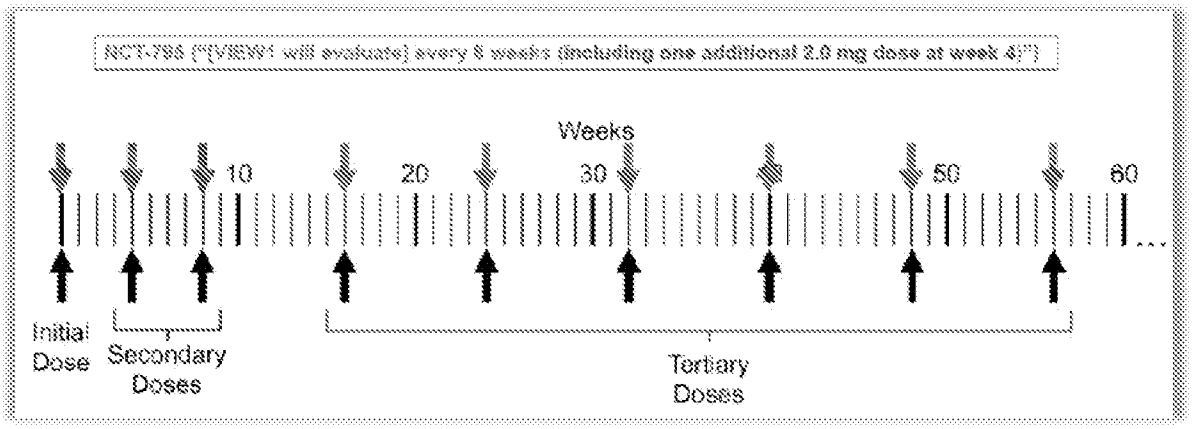
D. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00509795 (NCT-795) (Ex.1014).

1. Independent claim 1 of the '338 patent is anticipated by NCT-795.

267. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-795. As with the other references

above that disclose Regeneron's VIEW trials and the dosing regimens used in those trials, it is my opinion that NCT-795 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

268. For example, NCT-795 describes VIEW1 as a Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at week 4)." (Ex.1014, NCT-795, 8). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-795 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (blue arrows)

(i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

269. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-795, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[21]

[21] Regarding the preamble, *see, e.g.*, *supra* note 18.

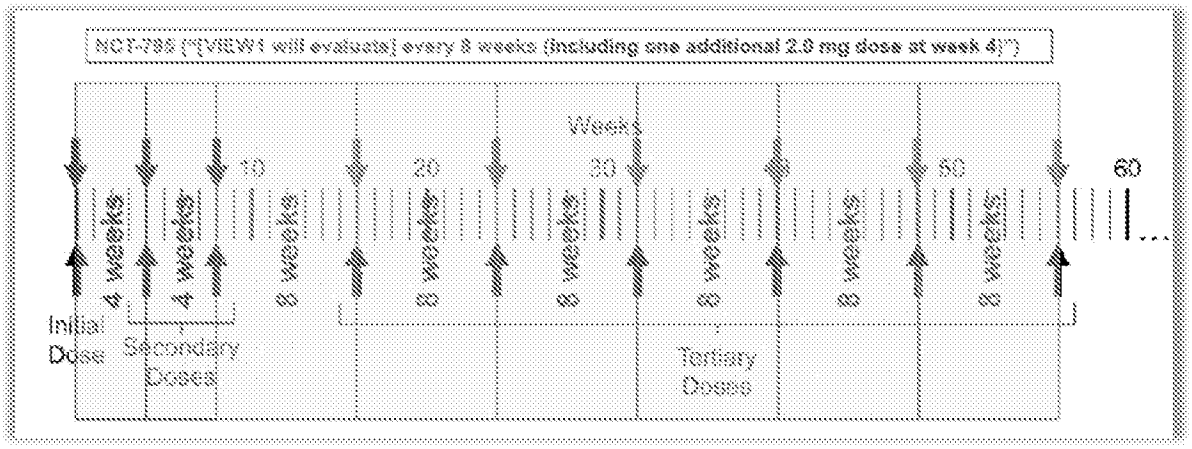
270. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by NCT-795.

2. Dependent claims 3 and 4 are anticipated by NCT-795.

271. Dependent claim 3 recites "[t]he method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

272. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

273. As illustrated in my modified Figure 1 of the '338 patent below, NCT-795 discloses the elements of claims 3 and 4. NCT-795 discloses a treatment arm wherein subjects are to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, NCT-795, 8). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:



(Ex.1001, '338 patent, Fig.1 (modifications added)).

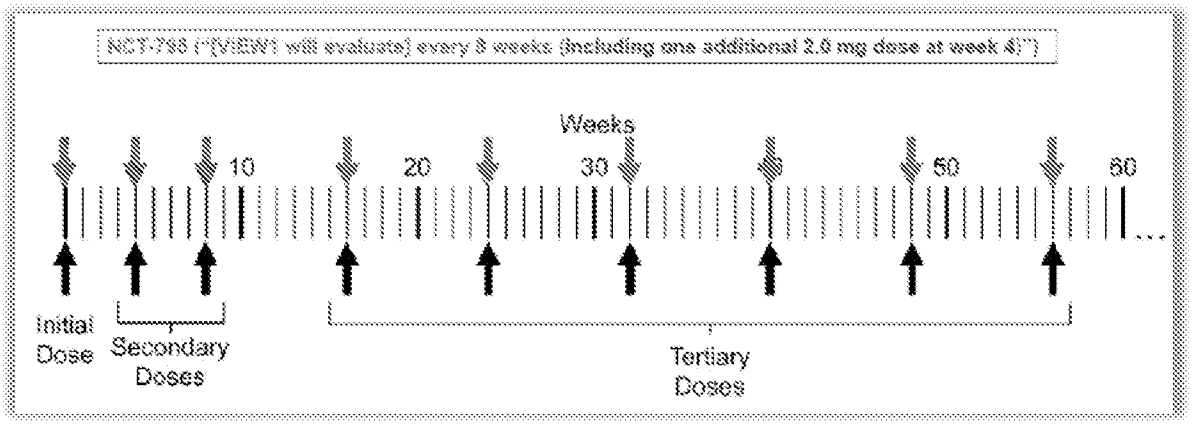
274. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-795.

3. Dependent claim 5 is anticipated by NCT-795.

275. For the same reasons as above for claims 3 and 4, NCT-795 discloses the elements of claims 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

276. NCT-795 discloses the clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As

illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

277. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-795.

4. Dependent claims 6 and 7 are anticipated by NCT-795.

278. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

279. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

280. NCT-795 discloses that the title of the Phase 3 clinical study is "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3). Thus, NCT-795 expressly discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

281. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-795.

5. Dependent claims 8-10 are anticipated by NCT-795.

282. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

283. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

284. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

285. NCT-795 discloses that the Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD." (Ex.1014, NCT-795, 3). NCT-795 therefore expressly discloses intravitreal administration.

286. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-795.

6. Dependent claims 11 and 13 are anticipated by NCT-795.

287. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

288. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

289. NCT-795 discloses Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses doses of claims 11 and 13.

290. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 8-10, it is my opinion that claims 11 and 13 are anticipated by NCT-795.

7. Independent claim 14 is anticipated by NCT-795.

291. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

292. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 267-70), it is also my opinion that NCT-795 discloses these identical elements in claim 14.

293. Second, in my opinion, NCT-795 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-795 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). .

294. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-795.

8. Dependent claims 16 and 17 are anticipated by NCT-795.

295. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

296. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

297. As discussed with respect to claims 3 and 4 above, NCT-795 discloses the elements of claims 16 and 17. (Ex.1014, NCT-795, 8). In my opinion, it was well established that the VIEW1 dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

298. Therefore, for these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by NCT-795.

9. Dependent claims 18 and 20 are anticipated by NCT-795.

299. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

300. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

301. As discussed with claims 6 and 7 above, NCT-795 discloses the title of the VIEW1 clinical study as "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3). NCT-795 therefore expressly discloses treating AMD, an angiogenic eye disorder.

302. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-795.

10. Dependent claim 19 is anticipated by NCT-795.

303. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

304. As discussed with claim 5, NCT-795 discloses that the VIEW1 clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye

administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As illustrated above in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses called for in the VIEW1 trial, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

305. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-795.

11. Dependent claims 21-23 are anticipated by NCT-795.

306. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

307. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

308. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

309. As discussed with claims 8-10 above, NCT-795 discloses that the VIEW1 Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD. (Ex.1014, NCT-795, 3). NCT-795 therefore discloses intravitreal administration of VEGF Trap-Eye/aflibercept.

310. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-795.

12. Dependent claims 24 and 26 are anticipated by NCT-795.

311. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

312. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

313. As discussed with claims 11 and 13 above, NCT-795 discloses VIEW1 Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses the claimed doses.

314. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-795.

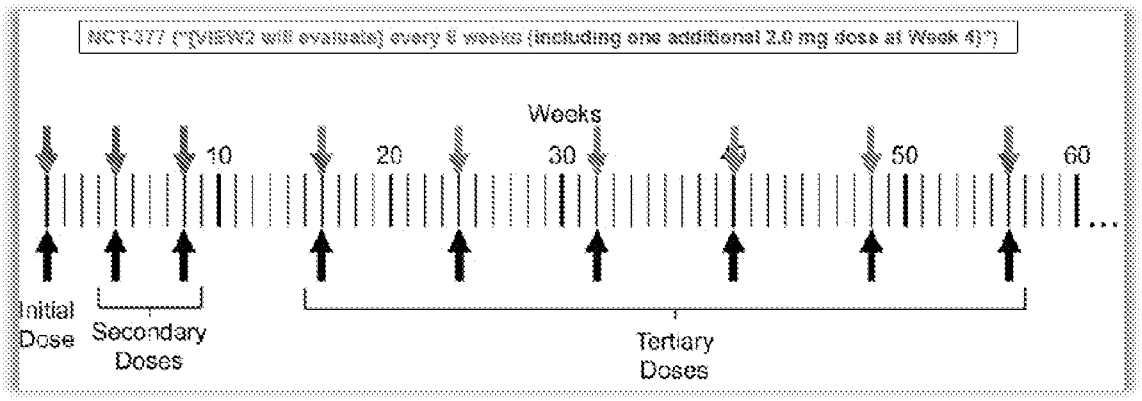
E. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00637377 (NCT-377) (Ex.1015).

1. Independent claim 1 of the '338 patent is anticipated by NCT-377.

315. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-377. As with the other references above that disclose Regeneron's VIEW trials and the dosing regimens used in those

trials, it is my opinion that NCT-377 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

316. For example, NCT-377 discloses the VIEW2 Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 5-6). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-377 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:



(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (blue arrows) (i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary

doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

317. NCT-377 further states that subjects will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." (Ex.1015, NCT-377, 6).

318. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-377, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and

VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[22]

319. For at least these reasons, it is my opinion that claim 1 is anticipated by NCT-377.

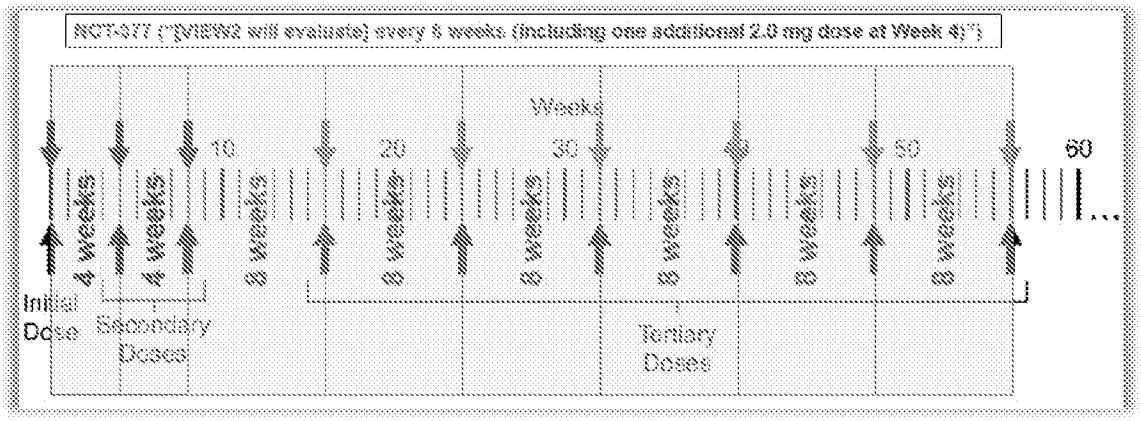
2. Dependent claims 3 and 4 are anticipated by NCT-377.

320. Claim 3 recites "[t]he method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

321. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

322. As illustrated in my modified Figure 1 of the '338 patent below, NCT-377 discloses the elements of claims 3 and 4. NCT-377 states that subjects in one of the four treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:

[22] Regarding the preamble, *see, e.g.*, *supra* note 18.



(Ex.1001, '338 patent, Fig.1 (modifications added)).

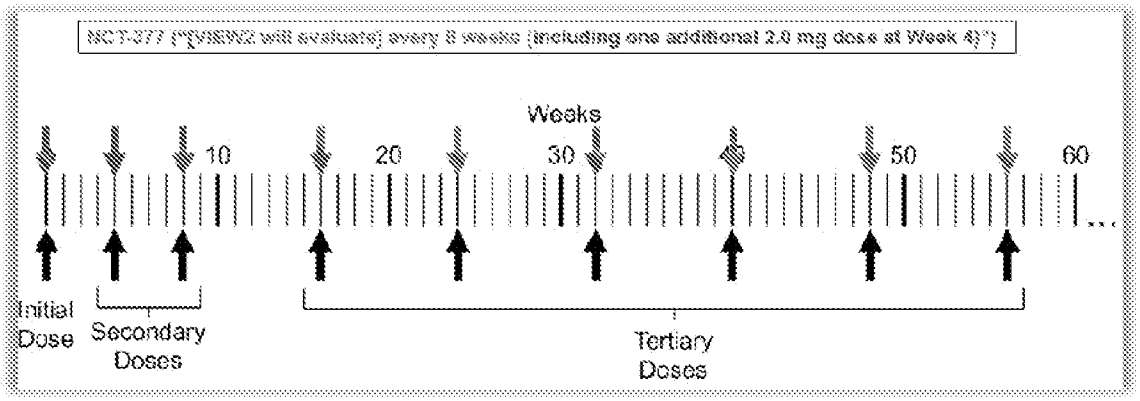
323. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-377.

3. Dependent claim 5 is anticipated by NCT-377.

324. For the same reasons as above for claims 3 and 4, NCT-377 discloses the elements of claim 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

325. NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week

dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):



(Ex.1001, '338 patent, Fig.1 (modifications added)).

326. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-377.

4. Dependent claims 6 and 7 are anticipated by NCT-377.

327. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of' several well-known eye disorders, including AMD.

328. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

329. NCT-377 discloses the title of the clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and

Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4). NCT-377 thus discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

330. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-377.

5. Dependent claims 8-10 are anticipated by NCT-377.

331. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

332. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

333. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

334. NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal* VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 thus expressly discloses intravitreal administration.

335. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-377.

6. Dependent claims 11 and 13 are anticipated by NCT-377.

336. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

337. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

338. NCT-377 discloses that subjects in one of the VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). NCT-377 thus expressly discloses the claimed doses.

339. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by NCT-377.

7. Independent claim 14 is anticipated by NCT-377.

340. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

341. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 315-19), it is also my opinion that NCT-377 discloses these identical elements in claim 14.

342. Second, in my opinion, NCT-377 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-377 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

343. Thus, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-377.

8. Dependent claims 16 and 17 are anticipated by NCT-377.

344. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

345. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

346. As discussed with respect to claims 3 and 4 above, NCT-377 discloses the elements of claims 16 and 17. NCT-377 states that subjects in one of the four VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). In my opinion, this VIEW2 dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year.

347. For these reasons, as well as the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 are anticipated by NCT-377.

9. Dependent claims 18 and 20 are anticipated by NCT-377.

348. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

349. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

350. As discussed with claims 6 and 7 above, NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4). NCT-377 therefore expressly discloses treating AMD, which was known to be an angiogenic eye disorder.

351. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-377.

10. Dependent claim 19 is anticipated by NCT-377.

352. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately

preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

353. As discussed with claim 5, NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

354. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-377.

11. Dependent claims 21-23 are anticipated by NCT-377.

355. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

356. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

357. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

358. As discussed with claims 8-10 above, NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal* VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 therefore expressly discloses intravitreal administration.

359. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-377.

12. Dependent claims 24 and 26 are anticipated by NCT-377.

360. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

361. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

362. As discussed with claims 11 and 13 above, NCT-377 discloses that subjects in one of the VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). NCT-377 therefore expressly discloses the claimed doses.

363. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-377.

F. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Obvious in View of Dixon, Either Alone or in Combination with the '758 Patent or Dix.

1. Independent claim 1.

364. I have set forth above the disclosures in Dixon that I believe anticipate the challenged claims, and I incorporate those disclosures herein. In my opinion, in addition to anticipating the challenged claims, Dixon also would make the subject matter of the challenged claims obvious.

365. First, one of ordinary skill in the art would have been motivated to explore dosing regimens that reduce the frequency of intravitreal injections administered in a monthly dosing scheme. This was a widely discussed concern at the time, and is evident from the Dixon reference itself. (Ex.1006, Dixon, 1574, 1577 (noting the "time and financial burden of monthly injections" and "[d]esirable attributes for emerging therapies for neovascular AMD include . . . decreased dosing intervals")).

366. Second, one of ordinary skill in the art would have observed in Dixon, and in the many other publicly available reports of the initiation of the VIEW Phase 3 trials, that a solution to the dosing frequency issue was presented therein in the

form of the publicly disclosed VIEW regimens involving every-8-week dosing following three monthly loading doses. (*Id.* at 1576).

367. Third, one of ordinary skill in the art would have had a reasonable expectation of success using the VIEW regimens for treating AMD. Dixon, in addition to reporting on the Phase 3 VIEW regimens, also provides a summary of the Phase 2 VEGF Trap-Eye results. For example, Dixon reports that the Phase 2 PRN regimen of 2.0 mg doses resulted in a mean increase of 9.0 ETDRS letters, with 29% gaining greater than or equal to 15 ETDRS letters at 52 weeks. (*Id.*). Those patients also experienced a mean decrease in retinal thickness of 143 µm. (*Id.*). A comparison to the results eventually reported for VIEW1/VIEW2 further illustrates why a person of ordinary skill in the art would have been justified in having a reasonable expectation of success based on the Phase 2 data:

Measure	Phase 2 4 monthly + PRN (as reported in Dixon)	Phase 3 (VIEW1, VIEW2) 3 monthly + every-8-week (as reported in Heier-2012)
BCVA letter gain	+9.0	+7.9, +8.9
Retinal thickness (µm)	-143	-128.5, -149.2
Number of doses (first year)	5.6	8

368. As Dixon further notes, patients on the Phase 2 PRN regimen received, on average, 1.6 doses during the PRN dosing phase. (*Id.*). This means that, combined with the 4 monthly loading doses, patients in this group received, on average, 5.6 doses over the course of the first year. On the other hand, a patient would receive 8 doses in the first year under the Phase 3 VIEW dosing regimen (3 monthly loading doses followed by 5 every-8-week doses (i.e., doses at months 0, 1, 2, 4, 6, 8, 10, and 12)). The reasonable expectation of success is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1). Indeed, after the Phase 2 results, Regeneron did in fact go with the 3 monthly loading dose/every-8-week dosing regimen for its Phase 3 trial. In my opinion, Regeneron would not have settled on that regimen without having a reasonable expectation that it would be successful. In sum, it is my opinion that a person of ordinary skill in the art, in light of the Phase 2 results, would have indeed had a reasonable expectation of success that the Phase 3 regimen would be capable of treating AMD.

369. Fourth, with respect to the amino acid sequence and protein domains recited in claim 1, I discuss these disclosures in depth in the sections above and incorporate that discussion into this analysis. VEGF Trap-Eye/aflibercept was a well-known molecule among those of ordinary skill in the art, and a description of its molecular structure and sequence could be found throughout the prior art. (*See,*

e.g., Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1093).

370. Accordingly, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 1 of the '338 patent obvious.

2. Dependent claims 3 and 4.

371. Dependent claim 3 limits the method of claim 1 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." And, claim 4 further limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

372. As discussed above, Dixon discloses the elements of claim 3 (each secondary dose is administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose) in the discussion of the VIEW study arms. (*See, e.g.*, Ex.1006, Dixon, 1576 ("2.0 mg at an 8 week dosing interval (following three monthly doses)")).

373. Accordingly, and for the reasons discussed above with respect to claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 3 and 4 of the '338 patent obvious.

3. Dependent claim 5.

374. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

375. Dixon discloses that the VIEW1 and VIEW2 clinical trials were to last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52* . . . ." (emphasis added)). As discussed above in the anticipation section, over the course of a year, and following the three monthly doses, the "8 week dosing interval" disclosed in Dixon for the VIEW studies would result in "at least 5 tertiary doses," administered at weeks 16, 24, 32, 40, and 48.

376. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 5 of the '338 patent obvious.

4. Dependent claims 6 and 7.

377. Claim 6 is dependent on claim 1 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

378. The Dixon reference is drawn to disclosures of VEGF Trap's use in treating AMD, which was known to be an angiogenic eye disorder. Dixon reported on the results of the Phase 1 and Phase 2 VEGF Trap-Eye AMD studies and set forth the dosing regimens being tested in the Phase 3 AMD trial, including the dosing regimen of 3 monthly doses followed by every-8-week dosing. (*See, e.g.*, Ex.1006, Dixon, 1576).

379. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and

nucleotide sequences in the '758 patent and Dix, makes claims 6 and 7 of the '338 patent obvious.

5. Dependent claims 8-10.

380. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

381. Claim 9 depends from claim 8 and specifies intraocular administration.

382. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

383. Dixon expressly discloses that the VEGF Trap was intravitreally administered, reporting that the VIEW1 and VIEW2 Phase 3 studies "will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye." (Ex.1006, Dixon, 1575-76 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye.

384. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 8-10 of the '338 patent obvious.

6. Dependent claims 11 and 13.

385. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

386. Dixon expressly discloses that the treatment arms in the VIEW studies will employ a 2.0 mg dose. (*See, e.g.*, Ex.1006, Dixon, 1576 (disclosing "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval (following three monthly doses)")).

387. Therefore, for these reasons, as well as the reasons set forth above for claims 1 and 10, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 11 and 13 of the '338 patent obvious.

7. Independent claim 14.

388. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

389. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after

the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 364-70), it is also my opinion that Dixon discloses these identical elements in claim 14.

390. Second, as discussed above, in my opinion, Dixon discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). Therefore, for the same reasons discussed above, it is my opinion that this aspect of claim 14 is obvious.

391. Therefore, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 14 of the '338 patent obvious.

8. Dependent claims 16 and 17.

392. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

393. I note that aside from the independent claims from which they depend, claims 16 and 17 are similar to claims 3 and 4. Accordingly, for the reasons discussed above for claim 14 and for claims 3 and 4, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 16 and 17 of the '338 patent obvious.

9. Dependent claims 18 and 20.

394. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the

angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

395. Aside from the independent claims from which they depend, claim 18 is similar to claim 7 and claim 20 is similar to claim 6. Accordingly, for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 18 and 20 of the '338 patent obvious.

10. Dependent claim 19.

396. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

397. Aside from the independent claims from which they depend, claim 19 is similar to claim 5. Accordingly, for the reasons discussed above for claims 5 and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 19 of the '338 patent obvious.

11. Dependent claims 21-23.

398. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

399. Claim 22 depends from claim 21 and specifies intraocular administration.

400. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

401. Aside from the independent claims from which they depend, claims 21-23 are similar to claims 8-10. Accordingly, for the reasons discussed above for claims 8-10, and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 21-23 of the '338 patent obvious.

12. Dependent claims 24 and 26.

402. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

403. Aside from the independent claims from which they depend, claims 24 and 26 are similar to claims 11 and 13. Accordingly, for the reasons discussed above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 24 and 26 of the '338 patent obvious.

IX. SECONDARY CONSIDERATIONS.

404. I understand that a patent owner may in some circumstances rely on so-called "secondary considerations of non-obviousness" to attempt to refute a finding of obviousness of a claim.[23] I also understand that there are several categories of secondary considerations, which might include alleged unexpected results or a "long-felt but unmet need." Notwithstanding that the unpatentability of the challenged claims is supported by strong evidence, including the numerous Regeneron disclosures and public announcements of its dosing regimens for VEGF Trap-Eye/aflibercept well prior to the filing date of the '338 patent, it is my opinion that there are no unexpected results or a "long-felt but unmet need" that would refute the strong case of obviousness against the challenged claims.

[23] I understand that any showing of "secondary considerations" by the patent owner is not relevant to an anticipation analysis.

405. For example, I was asked to review Regeneron's statement to the U.S. Patent and Trademark Office, dated September 11, 2015. Therein, Regeneron argues that "improved unexpected results" were observed and thereafter described in the working examples of the '338 patent and a 2012 publication reporting on the results of the VIEW studies (Ex.1019, Heier-2012). Regeneron characterizes the standard of care prior to the filing of the '338 patent as once per month dosing. (Ex.1017, '338 FH, 9/11/2015 Remarks, 6). They further characterize the results reported in Heier-2012 as surprising, dramatic, and unexpected since the every-eight-week dosing group exhibited outcomes similar to those receiving monthly injections.

406. First, I note that the applicants admit that the VIEW1/2 every-8-week dosing regimen falls squarely within the scope of the claims of the '338 patent. This is the same regimen that was disclosed and disseminated before the filing date of the '338 patent, as I discuss at length above. (*See, e.g.*, Ex.1006, Dixon; Ex.1007, Adis; Ex.1013, Regeneron (8-May-2008); Ex.1014, NCT-795; Ex.1015, NCT-377; and the detailed discussion above of the disclosures of the VIEW1 and/or VIEW2 studies in each of these references).

407. Second, in my experience and that a person of ordinary skill in the art, as of 2010, monthly dosing was not the regimen typically used in standard clinical practice. By 2010, as I discuss above, the discomfort, inconvenience, and risks

experienced by patients [24] receiving intravitreal injections led most in the ophthalmology community to reduce the frequency of administration whenever possible. For example, my typical practice, together with the typical practice of the skilled person, when administering intravitreal anti-VEGF agents, involved the administration of a few loading dose injections, typically spaced a month apart. Thereafter, we would usually bring back patients for monthly visits to assess visual acuity and retinal swelling and only administer injections on those monthly visits where there appeared to be loss in visual acuity or increase in retinal swelling.

408. Third, in addition to that approach being common practice among practicing ophthalmologists and persons of ordinary skill in the art, it was the trend among industry leaders at the time as well. For example, after Genentech's monthly dosing studies of ranibizumab (MARINA and ANCHOR), they embarked on a clinical trial campaign directed to investigating dosing regimens with less frequent injections. For example, Genentech began, as early as 2007, to assess dosing

[24] This is a point on which I agree with Regeneron. (*See, e.g.*, Ex.1017, '338 FH, 9/11/2015 Remarks at 6 (stating that once-per-month injections are "(1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event")).

regimens that included three monthly loading doses, followed by a period of individualized (i.e., as-needed/PRN) dosing, or fixed quarterly dosing. (*See, e.g.*, SUSTAIN (PRN dosing after 3 monthly loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO (PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses); Ex.1030, Mitchell, 6-7 (providing a summary of each of the above studies). From these studies, the authors concluded that while fixed quarterly dosing may be inferior to monthly dosing (though still more effective than placebo), the individualized regimens could achieve outcomes similar to that observed for monthly dosing. (*See, e.g.*, Ex.1030, Mitchell, 6-7).

409. Fourth, in my opinion, the results reported in Heier-2012, and which Regeneron relies upon in their remarks to the Patent Office, were not unexpected in light of the positive results reported for Regeneron's Phase 2 study of VEGF Trap-Eye in AMD. In that study, Regeneron used two treatment arms: (1) quarterly dosing for 12 weeks followed by PRN dosing; and (2) fixed monthly dosing for 12 weeks followed by PRN dosing. The latter group, when dosed with 2 mg, achieved on average a gain in visual acuity of 9 letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, Dixon, 1576). The results of the VIEW studies as reported in Heier-2012 included a mean gain in visual acuity of 7.9 letters and a mean decrease in retinal thickness of 128.5 μm. (Ex.1019, Heier-2012, 2542). In my opinion, these

results from the VIEW studies would not have been surprising or unexpected in light of the results reported for the Phase 2 CLEAR-IT-2 study. This is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1; *see also id.* ("Due to its high affinity for all isoforms of VEGF-A and PIGF . . . as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly . . . . These emerging Phase 2 clinical data seem to support the concept of durability of VEGF Trap-Eye.")).

410. Lastly, I disagree that there were "an infinite number of different treatment protocols" when deciding on dosing regimens to investigate. Given the concern (shared by Regeneron) over the frequency of monthly dosing, monthly injections would have been avoided if possible, and anything more frequent than monthly would not have been reasonably considered by skilled artisans. The ranibizumab studies were showing that quarterly (i.e., every 3 month) regimens had trouble maintaining gains in visual acuity in some cases. As a result, if monthly was disfavored, and every 3 months was seen as less effective in some cases, a person of ordinary skill in the art naturally would have considered dosing every 2 months, which is precisely what Regeneron used in their VIEW studies. Regarding the number of loading doses, the trend in the industry was that three monthly loading doses could achieve substantial gains in visual acuity and decreases in retinal

thickness. (*See, e.g.*, Ex.1030, Mitchell, 6-7). Therefore, in my opinion, there was nothing new or non-obvious about the regimen Regeneron settled upon, and its claims to the Patent Office that there were "an infinite number of different treatment protocols" was not true given the state of the art and the practical realities of treating AMD patients with intravitreal injections.

411. In sum, a person of ordinary skill in the art would have expected the claimed dosing regimen to work based on the positive Phase 1 and Phase 2 trial results. Thus, it would have been expected that following the dosing regimen set forth in the '338 patent would have led to at least some level of "treating" an angiogenic eye disorder. The dosing regimens claimed in the '338 patent were not unexpected in my opinion, and the arguments presented by the patentees to the Patent Office do not support their claims of unexpected results.

412. Moreover, to the extent that the inventors would claim an unmet and long-felt need was fulfilled with the '338 patent, in my opinion, this is not the case. While I agree that there may have been a need for VEGF antagonists prior to their development, in my opinion, once those antagonists were developed, and especially after the dosing knowledge was gleaned from ranibizumab and the early trials of VEGF Trap-Eye, arriving at a dosing regimen that extended the administration beyond once-monthly was obvious, had already been noted in the literature and put into actual practice, and served no "unmet" need. This is particularly so given that

the dosing regimen was already publicly disclosed as early as 2009, meaning that any "unmet" need had already been met by Regeneron's own public disclosures well before the '338 patent was filed.

413. I further understand that there may be commercial products that the patent owner may attempt to assert are encompassed by the claims, one potential example being Eylea®. However, in my opinion, none of the claimed dosing regimens covered by the '338 patent that I have discussed above are responsible for any commercial success of Eylea®, and I have seen no evidence that the commercial success of Eylea® has been due to anything outside of marketing and promotional activities or regulatory exclusivity. To the extent that Regeneron or their technical expert raise secondary considerations arguments, I reserve the right to address and respond to those arguments in a future declaration.

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

Dated: 5/4/21

By: _____
Dr. Thomas A. Albini

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2021-00881

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

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

DECLARATION OF MARY GERRITSEN, PH.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 9,254,338 B2

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I, Mary Gerritsen, Ph.D., declare as follows:

I. INTRODUCTION.

1. I submit this declaration on behalf of Mylan Pharmaceuticals Inc. ("Petitioner"). I understand that Petitioner is filing a petition with the United States Patent and Trademark Office ("USPTO") for *inter partes* review of U.S. Patent No. 9,254,338 B2 (the "'338 patent") (Ex.1001).

2. This Declaration contains my qualifications; my opinions based on my expertise, and my review of the '338 patent and other documents cited within this Declaration; the factual basis for those opinions; and data or other information I considered in forming my opinions. The opinions and facts set forth in this Declaration are based upon information and my analysis of documents related to the '338 patent, as well as my knowledge and experience in the pharmaceutical and biotechnology industries.

II. QUALIFICATIONS.

3. I am a pharmacologist with over thirty years of experience in the pharmaceutical and biotechnology industries.

4. In 2010, I founded Gerritsen Consulting, and I have been a consultant for the biotechnology industry on topics related to biotherapeutics and drug discovery in the therapeutic areas of oncology, immuno-oncology, ophthalmology, autoimmune diseases/inflammation, cardiovascular disease, and angiogenesis-

related diseases. Specifically, I have collaborated with companies in numerous areas of product development, including research strategy, target selection and assessment, preclinical pharmacology and mechanism of action studies, preparation of Investigational New Drug applications, procedures for clinical trials, and evaluation of pipeline portfolio strategies.

5. Prior to my consulting work, I was the Vice President of Molecular and Cellular Pharmacology at Exelixis, Inc. from 2004-2010. Exelixis is a biotechnology company focused on the development of small molecular therapeutics for the treatment of oncology and metabolic disease. I supervised many of the processes involved in preclinical to early clinical development, including target identification and validation, early lead discovery and validation, lead optimization, cellular and molecular pharmacology studies, pharmacodynamic assays, and early translational medicine studies. I also collaborated with the clinical groups in the early stages of Phase I clinical trials.

6. From 2003-2004, I was a consultant with Frazier Health Care Ventures in which I was involved in the founding of MacuSight, Inc., a pharmaceutical company focused on angiogenesis disorders, specifically focused on age-related macular degeneration and diabetic macular edema. I was an inventor on several of the patents that were the basis for the foundation of the company which included U.S. Patent Nos. 8,222,271, 8,486,960, and 9,452,156.

7. From 2002-2003, I was the Senior Director, Vascular Biology with Millennium Pharmaceuticals (formerly COR Therapeutics) where I was responsible for development of the strategic plan for vascular biology and oversaw numerous small molecule development programs in the therapeutic indications of atherosclerosis, peripheral vascular disease, and fibrosis.

8. Prior to the above, I was Associate Director of the Department of Cardiovascular Research at Genentech, Inc. from 1997-2001. Separately, I was a senior investigator in the angiogenesis group whose focus was the identification of novel targets for protein-based therapeutics. Throughout my time at Genentech, I was involved in the drafting and filing of over 1,000 patent applications in which over forty such applications issued as patents.

9. Before joining Genentech, I was a Principal Staff Scientist and Group Leader, Institute for Inflammation and Autoimmunity at Bayer Pharmaceuticals (formerly Miles Pharmaceuticals) from 1990-1997. During this time, I led the screening efforts for small molecule inhibitors of leukocyte adhesion, cyclo-oxygenase, and cytokine release/action while also supervising six laboratories within the Institute. Additionally, I developed collaborations with other industrial development laboratories as well as academic laboratories in order to promote advances in target discovery and assay development.

10. Prior to my roles in the pharmaceutical and biotechnology industry, I received a Bachelor of Science degree in Zoology and a Ph.D. in Endocrinology and Pharmacology from the University of Calgary. I completed my post-doctoral studies in Pharmacology at the University of California, San Diego. Following my post-doctoral work, I was an Assistant and later an Associate Professor of Physiology at New York Medical College from 1980-1989. During this time, I conducted research in therapeutic areas including stroke, inflammation, ophthalmology, and diabetic vascular disease.

11. Throughout my career, I have more than 100 publications in peer-reviewed journals, written numerous book chapters, and authored three books. I am currently, or have been, a member of numerous professional organizations, and I have been presented with numerous awards and honors throughout my career.

12. Additional information about my professional and educational experience, and other background information, is described in my *curriculum vitae* (Ex.1061).

III. SCOPE OF ENGAGEMENT.

13. I have been retained by Petitioner as a technical expert to offer my analysis and opinions regarding various issues related to certain prior art references as they relate to the '338 patent, discussed in more detail below.

14. My time spent on this project is compensated at $350 per hour. My compensation does not depend in any way on the outcome of Petitioner's petition for *inter partes* review of the '338 patent. Furthermore, I have no financial interest in this matter.

15. My opinions and views set forth in this Declaration are based on my education and training, my experience in academia and the pharmaceutical and biotechnology industries, and on the materials I have reviewed for this case.

16. I have reviewed the '338 patent and relevant sections of its prosecution history before the USPTO, (*see* Ex.1017, '338 FH). I have also reviewed and considered various other documents in arriving at my opinions, and cite them in this Declaration.

17. I have been asked to consider the level of education, skill set and training possessed by persons of ordinary skill in the field relevant to the '338 patent as of at least January 13, 2011.[1, 2]

18. I have also been asked to consider, from the perspective of the person of ordinary skill in the art as of at least January 13, 2011, whether certain references or documents were available as printed publications, or, in other words, whether certain references or documents would have been publicly accessible to persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, before 2011.

19. I have formed certain opinions on these issues, which I set forth in greater detail below. In sum, it is my opinion that each of the references I discuss in

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[1] I have been asked to assume that the priority date of the '338 patent is January 13, 2011, the date of the earliest filed provisional application that appears on the '338 patent cover page. However, I note that the Applicant of the application that issued as the '338 patent argued that the priority date of the '338 patent was November 2011. (*See* Ex.1017, '338 FH, 9/11/15 Amendment, 7). I have formed no opinion regarding the merit of the '338 patent's claim to any priority date.

[2] I provide my understanding of the qualifications for a person of ordinary skill in the art relevant to the '338 patent in ¶¶ 22-24, below.

this declaration are printed publications in that they were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before Jan. 13, 2011. Moreover, my opinions in this regard are repeatedly confirmed by other contemporaneous prior art documents, which expressly cite the references I have been asked to evaluate. (*See* ¶¶ 47, 54, 62, 73, 82-87, 97, below).

IV. THE PERSON OF ORDINARY SKILL IN THE ART.

20. As I mentioned above, it is my understanding that my analysis is to be conducted from the perspective of a person of ordinary skill in the art at the time of the invention.

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

22. I understand that a person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all pertinent art, thinks along the lines of conventional wisdom in the art, and is a person of ordinary creativity at the time of the invention. I further understand that the relevant timeframe for assessing the '338

patent's claims from the perspective of a person of ordinary skill in the art is assumed to be January 13, 2011 (the earliest possible priority date for the '338 patent).

23. With respect to the '338 patent, a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as age-related macular degeneration ("AMD"), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

24. A person of ordinary skill in the art would have been aware of the references and teachings described below, as well as other important information and references relating to angiogenic eye disorders, the causes of said disorders, and useful treatments for said disorders.

V. LEGAL STANDARDS.

25. I am not a lawyer and do not purport to offer any legal opinions. In forming my opinions set forth herein, I have been asked to apply certain standards regarding printed publications.

26. I understand that a reference, publication, document, etc. is a "printed publication" if the document is "publicly accessible." I also understand that a reference is considered "publicly accessible" if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

27. Thus, a reference that could be classified as a "printed publication" before the priority date of the '338 patent would be considered prior art to the '338 patent.

VI. U.S. PATENT NO. 9,254,338.

28. I understand that the '338 patent issued on February 9, 2016 to Regeneron Pharmaceuticals, Inc. and is titled "USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS," with George D. Yancopoulos listed as the sole inventor. (Ex.1001, '338 patent, cover). I also understand that the '338 patent issued from U.S. Application No. 13/940,370 ("the '370 Application"), a continuation-in-part of International Application No. PCT/US2012/020855, filed January 11, 2012, and claims priority to U.S. Provisional Application No.

61/432,245, filed on January 13, 2011, U.S. Provisional Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

29. I understand that the '338 patent contains two independent claims and twenty-four dependent claims. The independent claims are listed below:

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

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

(Ex.1001, '338 patent, 23:2-18; *id.*, 24:3-15 (emphasis added to highlight the differences between the claims)). Claim 14 is very similar to claim 1 with the only difference (highlighted in yellow) being that the VEGF antagonist (aflibercept) is described by reference to the nucleic acid SEQ ID NO rather than the amino acid SEQ ID NO as in claim 1. (*Id.*). I also understand that claims 2-13 depend from claim 1, directly or indirectly (*id.*, 23:19-24:2), and claims 15-26 depend from claim 14, directly or indirectly (*id.*, 24:16-53).

VII. PROSECUTION HISTORIES OF THE '338 PATENT AND ITS EUROPEAN EQUIVALENT, EP-325.

30. I have reviewed the prosecution history for the '338 patent, which I understand appears at Ex.1017. It is my understanding that the '370 Application was filed on July 12, 2013 (Ex.1017, '338 FH, 7/12/2013 Transmittal of New Application, 1) and originally included twenty claims directed towards a method of treating "an angiogenic eye disorder" with a "VEGF antagonist." (*Id.*, 7/12/2013 Original Application, 22-23).

31. I have also reviewed EP 2 663 325 (Ex.1062, EP-325), which appears to be the European equivalent to the '370 Application, which issued as the '338 patent. (*Id.*, cover). EP-325 claims the same priority chain as the '370 Application—specifically, EP-325 claims priority to International Application No. PCT/US2012/020855, filed January 11, 2012, that claims priority to U.S. Provisional Application No. 61/432,245, filed on January 13, 2011, U.S. Provisional

Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

32. As originally filed, it is my understanding that EP 325 included claims similar to those prosecuted in the '370 Application that issued as the '338 patent. (*See id.*, [0020]-[0024]; Ex.1063, EP-325-FH, 7/5/2013 Amendments, 19-20; Ex.1017, '338 FH, 7/12/2013 Original Application, 22-23). I have prepared the following chart to illustrate the similarities between the '370 Application claims and the EP 325 claims:

'370 Application Original Claims	**EP-325 Original Claims**
1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.	1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.
2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks	2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks

'370 Application Original Claims	EP-325 Original Claims
after the initial dose of the VEGF antagonist.	after the initial dose of the VEGF antagonist.
3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.	3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.
4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.	4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.
5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.	5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

'370 Application Original Claims	EP-325 Original Claims
6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.	6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.
7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.	7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration.
8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.	8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor based chimeric molecule.
9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.	9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.
10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.	10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.
11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a	11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a

'370 Application Original Claims	EP-325 Original Claims
multimerization component comprising amino acids 232-457 of SEQ ID NO:2.	multimerization component comprising amino acids 232-457 of SEQ ID NO:2.
12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.	12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.
13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.	13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
14. The method of claim 13, wherein the intraocular administration is intravitreal administration.	14. The method of claim 13, wherein the intraocular administration is intravitreal administration.
15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.	15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

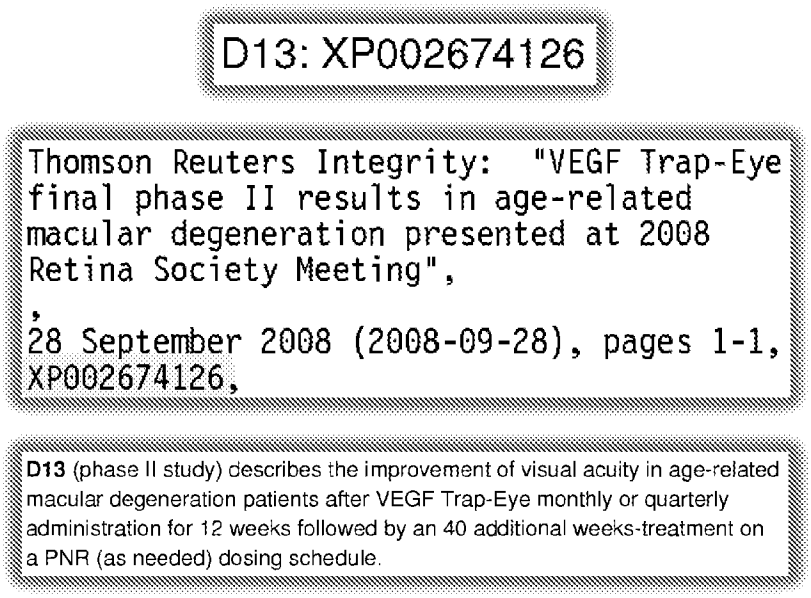
'370 Application Original Claims	EP-325 Original Claims
16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.	16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
17. The method of claim 16, wherein the intraocular administration is intravitreal administration.	17. The method of claim 16, wherein the intraocular administration is intravitreal administration.
18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.	18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.
19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.	19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.
20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.	20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

(Ex.1017, '338 FH, 7/12/2013 Original Application, 22-23; Ex.1063, EP-325-FH, 1/23/2012 Claims, 19-20).

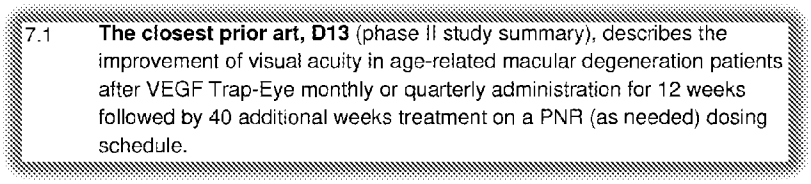
33. As I describe in more detail in the following paragraphs, several references were cited as prior art against EP-325, confirming, in my opinion their public availability and relevance to the '338 patent.

34. According to the prosecution history of EP-325, the International Searching Authority identified a September 28, 2008 Regeneron Press Release as a

"prior art document" that it "considered" in its May 22, 2012 written opinion (referencing the document as "D13")):



(Ex.1063, EP-325-FH, 5/14/2012 International Searching Authority Written Opinion, 3-4; *id.*, 7/19/2012 International Search Report, 1; *see also id.*, 9/5/2016 Third Party Observations, 2 (D13)). The International Search Authority then continued to discuss "D13" as the "closest prior art":



(*Id.*, 5/14/2012 International Searching Authority Written Opinion, 5).

35. The European Patent Office cited to this same Regeneron Press Release (as "D13") in reaching its conclusions in its August 21, 2014 Communication:

7.6	**The problem to be solved** *"provision of improved protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* has not been shown to be solved by the claimed solutions in the present application. The objective technical problem needs to be reformulated to the less ambitious one *"provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* for which the claimed solutions are obvious in view of D13.

(Ex.1063, EP-325-FH, 8/21/2014 Communication, 8; *see also id.*, 3-5).

36. Indeed, multiple Third-Party Observations were submitted during prosecution of EP 325. The first Third Party Observation included reference to, among other things, Regeneron Press Releases, a ClinicalTrials.gov record (VIEW2 study), and Regeneron's Form 10-Q from November 2007—all submitted as "prior art":

D13:	XP002674126
OBS1:	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008
OBS2:	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008
OBS3:	Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007
OBS4:	WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119
OBS5:	Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8
OBS6:	Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009
OBS7:	Mousa and Mousa, Biodrugs 2010; 24(3); 183-194
OBS8:	Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

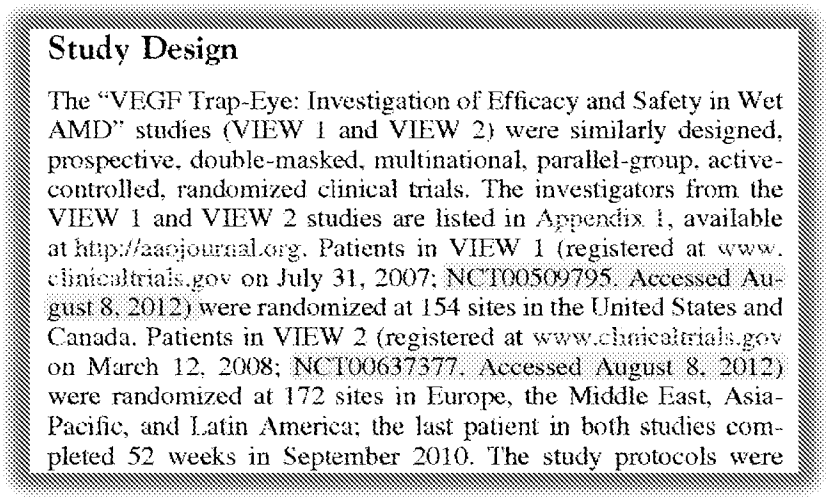
(Ex.1063, EP-325-FH, 9/5/2016 Third Party Observations, 2; *see also id.*, 3-4). The second Third Party Observation additionally identified the following:

Annex 1	Press Release of Regeneron dated 22 November 2010
Annex 2	Press Release of Regeneron dated 20 December 2010
Annex 3	Article in Retinal Physician (March 2010)

(*Id.*, 9/7/2016 Third Party Observations, 2).

37. The European Patent Office's and Third Parties' reliance on the above-mentioned documents confirms, in my opinion, that each was publicly accessible in that they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, could locate them. I further note that, as far as I can tell from reviewing the EP-325 file history, Regeneron never contested the public availability of those documents.

38. Separately, I find it important to note that, while prosecuting the '338 patent, the Applicants relied extensively on Heier-2012, a reference that, in my opinion, further confirms the public accessibility of Petitioner's asserted ClinicalTrials.gov reports, NCT-795, and NCT-377:



Study Design

The "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at http://aaojournal.org. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were

(Ex.1018, Heier-2012, 2539; *see also* Ex.1017, '338 FH, 9/11/2015 Amendment, 7 ("The attached Heier et al. article is a peer reviewed article published in 'Ophthalmology . . . .'")).

VIII. DISCLOSURES, KNOWLEDGE, & INFORMATION AVAILABLE IN THE ART BEFORE JANUARY 13, 2011.

A. REGENERON PRESS RELEASES.

39. In my experience in the pharmaceutical and biotechnology industries, companies like Regeneron and Bayer routinely issue press releases that include information on product development and/or clinical trials. These press releases can include information regarding, among other things, the specific product in development, the study design of a clinical trial, and preliminary or final results from a specific clinical trial or trials. A person of ordinary skill in the art would be interested in this type of information regarding ongoing product development within the industry, including information regarding the development of products of a direct

competitor. For example, this type of information continually updates the competitive landscape for a particular market and would assist the person of ordinary skill in the art in evaluating the same. As these press releases are a rich source of information about the ongoing development for a particular treatment, persons of ordinary skill in the art routinely review such press releases, whether as a result of exercising diligence, received from email alerts (e.g., Google Alerts), or website updates (e.g., Seeking Alpha, Evaluate Pharma, and FiercePharma). Indeed, I myself have searched for, reviewed and relied upon such press releases throughout my professional career.

40. Regeneron's and Bayer's press releases regarding VEGF Trap-Eye were no different, and, in my opinion, a person of ordinary skill in the art would have sought out this information. As specifically noted below, the Regeneron and Bayer press releases regarding VEGF Trap-Eye disclosed the ongoing development of VEGF Trap-Eye as a therapy for angiogenic eye disorders, including different treatment regimens using VEGF Trap-Eye.

41. Not only would a person of ordinary skill in the art have been interested in, and sought out, the information contained in the Regeneron and Bayer press releases, but this person would have been able to easily obtain these press releases directly from Regeneron's website on the date of each release. In fact, companies routinely publish press releases and other information on the company website under

a "News" menu or something similar (e.g., "Media" menu or "Investors & Media" menu) in order to disseminate them to the public in an easily accessible manner. Press releases are well-known to the community interested in the subject matter of the reference as a source of useful information. Additionally, documents such as press releases typically appear in web search results when a person of ordinary skill in the art conducts a search using various search engines (e.g., via Google, Google Scholar).

42. Thus, as of the date of each press release, a person of ordinary skill in the art would have been able to locate the specific press release on, among other things, Regeneron's website exercising reasonable diligence, easily access each press release via Regeneron's website, and easily download an electronic copy.

1. April 2008 Press Release.

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

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

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

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

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

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

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

(*Id.*, 1-2).

45. Regeneron (28-April-2008) added that VEGF Trap-Eye was being evaluated "using a monthly loading dose of . . . 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of . . . 2.0 mg every eight weeks." (*Id.*, 1-2).

46. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (28-April-2008) included the experimental group that received VEGF Trap-Eye 2.0 mg every eight weeks following 3 monthly "loading dose" injections. (*Id.*, 1-2).

47. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (28-April-2008) because it

pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (*Id.*, 1). My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis (Ex.1007, Adis) provides the following among twenty separate references to online "Media Releases":

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

(*Id.*, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-April-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g., id.*, 262-63, 268-69).

48. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-April-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[3] Thus, a person of

[3] *See, e.g.*, Ex.1012, Regeneron (28-April-2008), 1.

ordinary skill in the art could have easily accessed Regeneron (28-April-2008) via Regeneron's website and easily downloaded an electronic copy.

49. For at least these reasons, it is my opinion that Regeneron (28-April-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

2. May 2008 Press Release.

50. Regeneron and Bayer HealthCare AG issued a press release dated May 8, 2008 (Ex.1013, Regeneron (8-May-2008)) which described the phase 3 age-related macular degeneration VIEW 2 clinical trial. (*Id.*, 1; *see also* Ex.1032, Bayer (8-May-2008), 1).[4]

51. Specifically, Regeneron (8-May-2008) stated that both the complete VIEW 1 trial and the VIEW 2 trial were "designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks." (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1).

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

52. Regeneron (8-May-2008) also described the dosing regimens used in the VIEW 2 clinical trial, including "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four" in which one of the dosing arms included a regimen of 2 mg every 8 weeks, with an additional injection at week 4. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1-2).

53. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (8-May-2008) included the experimental group that received VEGF Trap-Eye 2 mg every other month following 3 initial monthly injections. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1-2).

54. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (8-May-2008) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with age-related macular degeneration. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

12. Bayer HealthCare AG. Bayer and Regeneron start additional Phase 3 Study for VEGF Trap-Eye in Wet Age-related Macular Degeneration. Media Release: 8 May 2008. Available from URL: http://www.bayerscheringpharma.de

13. Bayer HealthCare AG, Regeneron Pharmaceuticals Inc. Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration. Media Release: 8 May 2008. Available from URL: http://www.bayerhealthcare.com

(Ex.1007, Adis, 268 (emphasis added); *see also* Ex.1032, Bayer (8-May-2008), 1). Indeed, press releases such as Regeneron (8-May-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

55. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (8-May-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[5] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (8-May-2008) via Regeneron's website and easily downloaded an electronic copy.

[5] *See, e.g.*, Ex.1013, Regeneron (8-May-2008), 1.

56. For at least these reasons, it is my opinion that Regeneron (8-May-2008) and Bayer (8-May-2008) were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

3. September 2008 Press Release.

57. Regeneron and Bayer HealthCare AG issued a press release dated September 28, 2008 (Ex.1056, Regeneron (28-September-2008)) which described the final results for the same "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with wet age-related macular degeneration, treated with VEGF Trap-Eye that was described in Regeneron (28-April-2008). (*Id.*, 1).

58. As noted above, the patients in the study were "randomized to five dose groups" as follows:

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

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

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

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

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

(Ex.1056, Regeneron (28-September-2008), 1).

59. Regeneron (28-September-2008) stated that "[p]atients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline" and "mean decreases in retinal thickness versus baseline." (Ex.1056, Regeneron (28-September-2008), 1).

60. Regeneron (28-September-2008) also described the dosing regimens used in the two Phase 3 trials, VIEW1 and VIEW2, including "VEGF Trap-Eye dosed . . . 2 mg every 8 weeks (following three monthly doses)." (Ex.1056, Regeneron (28-September-2008), 1-2).

61. A person of ordinary skill in the art would have understood the dosing regimens disclosed in Regeneron (28-September-2008) included the experimental groups that were to receive VEGF Trap-Eye 2 mg every 8 weeks (following three monthly doses) or "monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye" followed by "a PRN dosing schedule based upon the physician assessment of the need for re-treatment." (Ex.1056, Regeneron (28-September-2008), 1-2).

62. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (28-September-2008) because it

pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1056, Regeneron (28-September-2008), 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adi provides the following among twenty separate references to online "Media Releases":

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

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-September-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g., id.*, 262-63, 268-69).

63. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-September-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter

contained therein without further research or experimentation.[6] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (28-September-2008) via Regeneron's website and easily downloaded an electronic copy.

64. For at least these reasons, it is my opinion that Regeneron (28-September-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

4. Additional Regeneron Press Releases.

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

66. The patients in the study were "randomized to 5 groups" where "[t]wo groups received either 0.5 or 2.0 mg of VEGF Trap-Eye administered every four weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye." (Ex.1053, Regeneron (27-March-2007), 1). Furthermore, the President of Regeneron Research Laboratories was quoted as stating "[o]ur Phase 3 program is

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

being designed to test this possibility and further evaluate the safety and efficacy of various doses and dosing intervals of the VEGF Trap-Eye." (*Id.*).

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

68. Regeneron and Bayer HealthCare AG issued a press release dated August 19, 2008 (Ex.1089, Regeneron (19-August-2008)), which described the 52-week data for the same "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with "wet age-related macular degeneration (AMD)" treated with VEGF Trap-Eye that was described in Regeneron (28-April-2008). (*Id.*, 1; *see also* Ex.1092, Bayer (19-August-2008), 1).

69. As noted above, the patients in the study were "randomized to five dose groups" as follows:

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

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

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

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

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

(Ex.1089, Regeneron (19-August-2008), 1; Ex.1092, Bayer (19-August-2008), 1-2).

70. Regeneron (19-August-2008) also described the dosing regimens used in the two Phase 3 trials, VIEW 1 and VIEW 2, including "VEGF Trap-Eye dosed . . . 2 mg every 8 weeks (following three monthly doses)." (Ex.1089, Regeneron (19-August-2008), 1; Ex.1092, Bayer (19-August-2008), 2-3).

71. Regeneron issued a press release dated September 14, 2009 (Ex.1068, Regeneron (14-September-2009)), which described two "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1). Specifically, Regeneron (14-September-2009) described "VEGF Trap-Eye . . . dosed . . . 2.0 mg every eight weeks (following three monthly doses)." (*Id.*).

72. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in at least Regeneron (19-August-2008) and Regeneron (14-September-2009) included the experimental group that was to receive VEGF

Trap-Eye "2 mg every 8 weeks (following three monthly doses)." (Ex.1089, Regeneron (19-August-2008), 1; *see also* Ex.1068, Regeneron (14-September-2009), 1 ("2.0 mg every eight weeks (following three monthly doses)").

73. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in the above Press Releases because they pertain to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (*See* ¶¶ 40-41, 47, 54, 62, above). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

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

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron's Press Releases were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g., id.*, 262-63, 268-69).

74. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate these Regeneron Press Releases exercising reasonable diligence, which would have at least led the person of ordinary

skill in the art to Regeneron's website where these documents were easily accessible and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[7] Thus, a person of ordinary skill in the art could have easily accessed these Press Releases via Regeneron's website and easily downloaded an electronic copy.

75. For at least these reasons, it is my opinion that Regeneron's Press Releases outlined above were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

B. CLINICALTRIALS.GOV.

76. ClinicalTrials.gov is an electronic registry and results database of clinical studies supported by the U.S. National Institutes of Health that is open and accessible to the public as a "resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and

[7] *See, e.g.*, Ex.1053, Regeneron (27-March-2007), 1; Ex.1054, Regeneron (2-August-2007), 1; Ex.1089, Regeneron (19-August-2008), 1; Ex.1068, Regeneron (14-September-2009), 1.

conditions."[8] Each study record includes a summary of the study protocol. ClinicalTrials.gov includes records for several clinical studies involving aflibercept, namely VIEW1 (ClinicalTrials.gov identifier NCT00509795) (Ex.1014, NCT-795), and VIEW2 (ClinicalTrials.gov identifier NCT00637377) (Ex.1015, NCT-377).

77. In my experience, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials. The information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.[9] Clinical trials are submitted to the site when they begin, and the information on the site is updated throughout the study.[10] Indeed, I myself have searched for, reviewed and relied upon the information found in numerous clinical trials through ClinicalTrials.gov. Furthermore, a person of ordinary skill in the art considers the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative.

78. NCT-795 was first available as of at least August 1, 2007 and describes a clinical study titled "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal

[8] Ex.1069, Background-ClinicalTrials.gov.

[9] *Id.*

[10] *Id.*

VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3; Ex.1087, Wayback-Affidavit-038 (Wayback Machine records showing public availability of NCT-795 prior to Jan. 13, 2011); Ex.1018, Heier-2012, 2539 ("Patients in View 1 (registered at www.clinicaltrials.gov on July 31, 2007 . . .)")). NCT-795 lists the following experimental "arms" of the study:

Experimental Arm 1: aflibercept injection 0.5mg (VEGF Trap-Eye)	0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental Arm 2: aflibercept injection 2.0mg (VEGF Trap-Eye)	2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental Arm 3: aflibercept injection 2.0mg (VEGF Trap-Eye)	2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

(Ex.1014, NCT-795, 6-8 (Experimental Arms 1-3)). The experimental arms above included the group which required participants to receive "2.0 mg VEGF Trap-Eye

administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (*Id.*, 8).

79. NCT-377 was first available as of at least March 18, 2008 and describes a clinical study titled "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4; Ex.1087, Wayback-Affidavit-038 (Wayback Machine records showing public availability of NCT-377 prior to Jan. 13, 2011); *see also* Ex.1018, Heier-2012, 2539 ("Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008 . . .)."")). NCT-377 lists the following experimental "arms" of the study:

Experimental Arm 1: Aflibercept Injection (VEGF Trap-Eye)	0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental Arm 2: Aflibercept Injection (VEGF Trap-Eye)	2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.

	Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental Arm 3: Aflibercept Injection (VEGF Trap-Eye)	2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

(Ex.1015, NCT-377, 6 (Experimental Arms 1-3)). The experimental arms above included the group which required participants to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year." (*Id.*, 1).

80. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in NCT-795 and NCT-377 included the experimental group that received VEGF Trap-Eye 2.0 mg every two months "including one additional 2.0 mg dose at Week 4." (Ex.1014, NCT-795, 8; *see also* Ex.1015, NCT-377, 6).

81. A person of ordinary skill in the art would have been interested in and easily accessed and sought out the information disclosed on the ClinicalTrials.gov

website regarding NCT-795 and NCT-377 because it pertains to ongoing routine product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1014, NCT-795, 6-8; Ex.1015, NCT-377, 6). Thus, in my opinion, NCT-795 and NCT-377 were both "publicly accessible" as they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, could locate them.

82. My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly cited to clinical trial records from ClinicalTrials.gov, including both NCT-795 and NCT-377. For example, Reichert (Ex.1072, Reichert)[11] provides the following disclosures of NCT-795 and NCT-377:

[11] Ex.1072, Reichert, 76; *see also id.*, cover (Reichert is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

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

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

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

(*Id.*, 95 (emphasis added); *see also id.*, 96). Moreover, Reichert makes multiple, express references to obtaining information online directly from ClinicalTrials.gov. (*Id.*, 79 (Table 7 ("listed on clinicaltrials.gov")); *id.*, 99 (Ref. No. 69 (citing ClinicalTrials.gov record and corresponding internet address))).

83. Similarly, Anderson (Ex.1073, Anderson)[12] provides the following disclosures of NCT-795 and NCT-377 online reports:

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

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

84. Another example, Ciulla (Ex.1074, Ciulla),[13] provides the following:

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[12] Ex.1073, Anderson, 272 (Anderson is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

[13] Ex.1074, Ciulla, 158 (Ciulla is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

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

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

85. Ni (Ex.1075, Ni)[14] provides the following:

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

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

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

[14] Ex.1075, Ni, 401 (Ni is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

86. Another example, Zarbin (Ex.1076, Zarbin),[15] provided the following:

> in a Phase 1 clinical trial.[130] VEGF Trap-Eye (http://clinicaltrials.gov/ct2/show/NCT00509795?term=VEGF+Trap-Eye&rank=14) is formulated for intravitreal injection, appears to be effective in a Phase 2 trial (www.bmctoday.net/retinatoday/2009/10/article.asp?f=1009_08.php), and is now being compared with ranibizumab in a Phase 3 clinical trial. AAV2-sFLT01

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

87. Dixon (Ex.1006, Dixon)[16] provides the following citations, further confirming that both NCT-795 and NCT-377, including the dosing regimens disclosed therein, were publicly available as of at least September 28, 2008:

[15] Ex.1076, Zarbin, 1350 (Zarbin is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

[16] Ex.1006, Dixon, 1573 (Dixon is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

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

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

(*Id.*, 1579 (emphasis added)). Accordingly, it is my firm opinion that ClinicalTrials.gov records, NCT-795 and NCT-377, were well-known—and widely available—to the community interested in the subject matter of the '338 patent.

88. Prior to 2011, a person of ordinary skill in the art would have also been able to locate both NCT-795 and NCT-377 exercising reasonable diligence and which would have at least led the person of ordinary skill in the art to the ClinicalTrials.gov website where the documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[17] Thus, a person of ordinary

[17] *See* Ex.1014, NCT-795, 1; Ex.1015, NCT-377, 1.

skill in the art of the '338 patent could have easily accessed both NCT-795 and NCT-377 via ClinicalTrials.gov and easily downloaded an electronic copy of each.

89. For the reasons outlined above, a person of ordinary skill in the art would have considered the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative and it is my opinion that NCT-795 and NCT-377 were both well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

C. SEC FILINGS.

90. As I note above (*see* ¶¶ 39-41), company press releases were well-known, and widely available, to persons of ordinary skill in the art. This was especially true of persons of ordinary skill in the art of the '338 patent, who expressly cited Bayer and Regeneron press releases. (*See, e.g.*, Ex.1007, Adis, 262-63, 268-69).

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

considered to be among the most accurate and reliable . . . sources of information available"); Ex.1079, Kuepper).

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

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

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

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

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

95. Second, in my opinion and as I noted above, a person of ordinary skill in the art would have been aware of such company filings, such as Regeneron's September 30, 2009 10-Q (Ex.1021, 2009 10-Q), and would routinely look to 10-Q filings to determine what drugs and treatments pharmaceutical companies were working on. Here, Regeneron disclosed information regarding, among other things, its ongoing development of the VEGF Trap-Eye program—specifically focused on the clinical trials for VEGF Trap-Eye—in its September 30, 2009 10-Q. (*Id.*, 20 ("The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of . . . 2.0 mg at a dosing interval of eight weeks (after three monthly doses)."). 2009 10-Q also disclosed results of the CLEAR-IT trial, which included "monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing," and the DA VINCI trial. (*Id.*, 19-20).

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

97. Thus, in my opinion, a person of ordinary skill in the art also would have been interested in, and sought out, the information disclosed in 2009 10-Q because it pertains to ongoing product development within the industry, including

dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with angiogenic eye disorders such as wet AMD. (Ex.1021, 2009 10-Q, 19-20). My opinion in this regard is confirmed by other contemporaneous prior art to the '338 patent which expressly refer to the Regeneron 2010 Financial Press Release which, in turn, directed a person of ordinary skill in the art to Regeneron's company filings with the SEC. (*See* Ex.1007, Adis, 268 (Ref. Nos. 6, 18)). Indeed, company filings such as 2009 10-Q were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See id.*, 262-63, 268 (Reference Nos. 6, 18)).

98. It is also my opinion that 2009 10-Q would have been routinely available to a person of ordinary skill in the art. Prior to 2011, a person of ordinary skill in the art would have been able to locate 2009 10-Q exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[18] Thus, a person of ordinary skill in the art could have easily accessed 2009 10-Q via Regeneron's website and easily downloaded an electronic copy.

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

99. For at least these reasons, it is my opinion that 2009 10-Q was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

IX. CONCLUDING STATEMENTS.

100. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the USPTO Patent Trial and Appeal Board. I acknowledge that I may be subject to cross-examination in this case. If cross-examination is required of me, I will appear for cross-examination during the time allotted for such cross-examination.

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

Dated: April 26, 2021

Mary Gerritsen, Ph.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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

EXPERT DECLARATION OF DR. DIANA V. DO, M.D.

TABLE OF CONTENTS

I, Dr. Diana Do, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. ("Regeneron") as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials I have reviewed in relation to the Petition for *Inter Partes* review ("IPR") of U.S. Patent No. 9,254,338 (the "'338 patent") (Ex. 1001), in particular how a person of skill in the art as of the filing date of the '338 patent would understand certain terms of the '338 patent claims, and responses to the opinion and views of Petitioner's declarant, Dr. Thomas A. Albini. I submit this declaration in support of Regeneron's Patent Owner Preliminary Response ("POPR"). I reserve the right to provide further and additional opinions in the event that IPR is instituted.

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

II. QUALIFICATIONS AND EXPERIENCE

3. I am a Professor of Ophthalmology and the Vice Chair for Clinical Affairs at the Byers Eye Institute at Stanford University School of Medicine and have been since 2017. I also serve as a Physician Improvement Leader at Byers Eye Institute, a position I have held since 2018. I have an active clinical and surgical practice and I work as a clinical investigator to study novel treatments for retinal diseases. In addition, I teach students, residents, and retina fellows at Stanford and

am a member of the Stanford Ophthalmology Education Committee.

4. I graduated from the University of California Berkeley (summa cum laude) with a B.A. degree in Molecular and Cellular Biology in 1995 and earned my M.D. (Alpha Omega Alpha) from the University of California San Francisco School of Medicine in 1999. Following medical school, I completed an internship in internal medicine at Massachusetts General Hospital at Harvard Medical School. From 2000-2003, I completed my residency in Ophthalmology at the Wilmer Eye Institute at Johns Hopkins University School of Medicine, and then remained at the Wilmer Eye Institute for a Retina Fellowship in surgical and medical retina from 2003-2005.

5. From 2005 through 2010, I served as Assistant Professor of Ophthalmology and Assistant Head of the Retina Fellowship Training Program at the Wilmer Eye Institute. In 2011, I was promoted to Associate Professor and Head of the Retina Fellowship Training Program, positions I held through 2013.

6. In 2013, I joined the faculty at the Truhlsen Eye Institute at the University of Nebraska College of Medicine, where I became a full Professor of Ophthalmology in 2015. At the Truhlsen Eye Institute, I was Head of the Retina Fellowship Training Program and Program Director for the Ophthalmology Residency. In my leadership roles at the Truhlsen Eye Institute, I also served as Vice Chair of Education. I was recruited by Stanford University's Ophthalmology

Department (the Byers Eye Institute) at Stanford in the beginning of 2017.

7. As a physician-scientist, I am an international leader in the treatment of diabetic retinopathy and wet AMD ("wAMD"). My research has led to more than 140 peer-reviewed publications. My research interest focuses on evaluating the efficacy and safety of novel pharmacologic therapies for diabetic macular edema, diabetic retinopathy, wAMD, retinal vein occlusion, and ocular inflammation. I have led national and global clinical trials investigating intravitreal VEGF inhibitors (aflibercept and ranibizumab) for diabetic eye disease and wet AMD. Our research developed a greater understanding of how intraocular inhibition of VEGF reduces vascular permeability and angiogenesis in diabetic eye disease, thereby reducing diabetic macular edema and improving visual acuity. Before the onset of pharmacologic therapies, thermal laser photocoagulation was the only treatment option for diabetic macular edema and laser was not effective in improving vision. Our research led to new treatment paradigms and better vision outcomes for patients with diabetic macular edema, diabetic retinopathy, and wAMD. The results from the collaborative research that I led has revolutionized how ophthalmologists throughout the world think about and treat patients with VEGF-mediated retinal diseases.

8. Since 2009, I have been the lead investigator and a Steering Committee member for the evaluation of aflibercept, a fusion protein that inhibits VEGF, in

diabetic macular edema. I initiated the first-in-human clinical trial of aflibercept. In addition, I also was the principal investigator on the Phase II and III clinical trials of aflibercept for diabetic macular edema to further evaluate efficacy, dosing regimens, and safety. My leadership in these global clinical trials, which enrolled over 1,000 subjects, contributed to FDA approval of aflibercept for diabetic macular edema. Aflibercept has also been approved by FDA for other angiogenic ocular diseases such as wAMD, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

9. My research efforts have also led to a greater understanding of the role of ranibizumab, an intravitreal VEGF antibody fragment biologic, in diabetic macular edema. I was a lead investigator in the Ranibizumab for Edema of the Macula in Diabetes (READ) Study Group and was the lead author on multiple manuscripts evaluating the efficacy and safety of ranibizumab. The collaborative studies that I led contributed to understanding dosing regimens for intravitreal VEGF inhibitors, and led to the design of pivotal clinical trials involving ranibizumab for diabetic macular edema. Ranibizumab was the first FDA approved intravitreal VEGF inhibitor for diabetic macular edema, and helped to transform the management of diabetic retinopathy. I continue to lead clinical trials investigating new treatments for retinal diseases.

10. As a result of my research, I am recognized as an international thought

leader on the subject of the retina and am regularly invited to lecture and teach at international and national meetings including the American Academy of Ophthalmology Retina Sub-Specialty Meeting, American Society of Retina Specialists, Asian Pacific Vitreo-Retinal Society Meeting, Canadian Ophthalmology Society Meeting, and congresses throughout Europe. I have organized and participated as a faculty member in national continuing medical education courses to teach my retina colleagues how to manage and treat diabetic macular edema, wet AMD, retinal vein occlusion, diabetic retinopathy, and other retinal disorders. Furthermore, I have held leadership positions at the American Society of Retina Specialists (Communications Committee Member to curate and develop online educational material), Women in Retina (Board Member and Secretary), Maryland Eye Society (President).

11. I am a practicing ophthalmologist with over 15 years of clinical and surgical practice in retina. I am a leader in the management of diabetic retinopathy, the leading cause of blindness in working age adults, and wAMD, the leading cause of vision loss in elderly individuals in developed countries. I have a high-volume clinical and surgical practice and spend approximately 1.5 days per week in clinic at the Byers Eye Institute and half-day per week at the Santa Clara Valley County Medical Center seeing patients in my clinical practice. In addition, I operate approximately one day per week at the Byers Eye Institute.

12. Given my extensive experience and research on diabetic retinopathy and wAMD, I have become the expert retinal specialist and surgeon in our department for evaluating these chronic eye diseases. Since joining Stanford's Ophthalmology Department, I have also become one of the highest volume retina surgeons among our faculty. Because proliferative diabetic retinopathy can lead to tractional retinal detachment and bleeding within the eye, I am referred complex cases that often require clinic-based treatments (such as intravitreal injections of medicines or pan retinal laser photocoagulation) or surgical management. Since I have clinical and research expertise using intravitreal vascular endothelial growth factor (VEGF) inhibitors in wAMD, ophthalmologists refer patients to me for consultation or co-management, particularly of chronic cases that have not responded to therapy. The majority of my patients are from the Bay Area or central California, and approximately 10% travel from more than 5 hours away to seek my expert opinion. I have been recognized as a "Top Doctor" in the Bay Area for the past three years.

13. A current copy of my curriculum vitae is included at Ex. 2002.

III. SUMMARY OF OPINIONS

14. My opinions and views set forth in this declaration are based on my education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases, as well as the materials I reviewed in

preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '338 patent at the time of its earliest priority application.

15. In forming my opinions, I have reviewed the following materials: (a) the Petition for *Inter Partes* Review of the '338 patent, IPR2021-00881, including all cited exhibits, (b) all priority applications leading to the issuance of the '338 patent, (c) all other documents and references herein, and (d) the Patent Owner's Preliminary Response to which my declaration relates.

16. It is my opinion, for at least the reasons set forth below, that the preamble language of Claims 1 and 14 requires treatment of an angiogenic eye disorder.

17. Further it is my opinion, for the reasons set forth below, that "tertiary dose(s)" means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

IV. THE PERSON OF ORDINARY SKILL IN THE ART

18. For the limited purpose of preparing this declaration in support of Patent Owner's Preliminary Response, I have been asked to apply Dr. Albini's definition of a person of ordinary skill in the art (who I also refer to as the "skilled artisan"):

> [A] person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or

> published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Ex. 1002, ¶ 28.

19. Applying Dr. Albini's definition a person of ordinary skill in the art, I would have been at least a skilled artisan when the '338 patent was filed.

20. Likewise, for the purpose of preparing this declaration, I have been informed and understand that the earliest filing date of the '338 patent is January 13, 2011, based on the filing of a Provisional Application on that date.

V. THE '338 PATENT

21. I understand that Petitioner has challenged claims 1, 3-11, 13-14, 16-24 and 26 of the '338 patent.

A. Claim 1

22. The '338 patent has two independent claims, claim 1 and 14.

23. Claim 1 recites:

> A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

Ex. 1001 at 23:1-18.

24. The dosing regimen of Claim 1 is directed to the treatment of any type of angiogenic eye disorder with a VEGF antagonist that has a particular amino acid sequence.

25. The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.

26. Challenged claims 3-11 and 13 depend from Claim 1, and further limit the timing between dosage administration, the specific angiogenic eye disorder, administration route, and dosage amount.

B. Claim 14

27. Claim 14 recites:

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

Ex. 1001 at 24:3-15.

28. The dosing regimen of Claim 14 is directed to the treatment of any type of angiogenic eye disorder with a particular VEGF antagonist that is encoded by the recited nucleic acid sequence.

29. Like Claim 1, the dosing regimen of Claim 14 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.

30. Thus, Claim 14 differs from Claim 1 only with respect to the last

"wherein clause" specifying the nucleic acid sequence of SEQ ID NO:1. I understand that SEQ ID NO:2 is the corresponding amino acid sequence of the nucleic acid sequence SEQ ID NO:1.

31. Challenged Claims 16-24 and 26 depend from Claim 14, and further limit the timing between dosage administration, the specific angiogenic eye disorder, administration route, and dosage amount.

VI. LEGAL FRAMEWORK

32. For purposes of this declaration, I have been informed by counsel for Patent Owner about certain aspects of the law that are relevant to my analysis and opinions.

33. I understand from counsel for Patent Owner that patent claim terms are construed from the vantage point of a skilled artisan to which the invention relates at the time of the invention (or as of the effective filing date of the patent application).

34. I am informed by counsel that claim terms should be considered in the context of the entire patent claim where they appear, as well as in the context of the other claims, the specification, and the prosecution history of the patent at issue (collectively, "intrinsic evidence"), taken as a whole (as opposed to in isolation and/or out of context).

35. I am advised by counsel that absent an explicit statement to the contrary by the patent applicant, a patent claim term should have its full ordinary and customary meaning and not be limited to a specific example that may appear in the patent specification as referring to a preferred embodiment.

36. I have been informed that where a term has no ordinary and customary meaning to those of ordinary skill in the prior art, one looks to the specification in the patent.

37. I am advised it is only necessary to construe terms that are in controversy, and only to the extent necessary to resolve the controversy.

VII. CLAIM CONSTRUCTION

38. I have been asked to consider the meaning of "[a] method for treating an angiogenic eye disorder in a patient" and "tertiary dose(s)" from the perspective of a skilled artisan as of January 13, 2011, and respond to Dr. Albini's opinions regarding the meaning of these terms.[1]

A. "A method for treating an angiogenic eye disorder in a patient"

39. The preamble of Claims 1 and 14 recites "[a] method for treating an angiogenic eye disorder in a patient." Ex. 1001 at 23:2-3, 24:3-4.

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[1] I note that in this declaration I am specifically responding to Dr. Albini's opinions with respect to claim construction only. I reserve the right to provide further opinions both with respect to claim construction and to respond to additional statements and opinions set forth in Dr. Albini's declaration if this *inter partes* review is instituted.

40. Dr. Albini states that the preamble language "method for treating" simply means "administering a therapeutic agent to a patient." Ex. 1002, ¶ 43. This, however, ignores the remaining language in the preamble which specifies what is being treated: "an angiogenic eye disorder in a patient." No ordinarily skilled artisan would think that this language encompasses administering the specified treatment to a person suffering, for example, solely from arthritis. Nor would the ordinarily skilled artisan think that the administration of an infinitesimal amount of the specified compound is encompassed by the claim. Neither would constitute a "method for treating an angiogenic eye disorder in a patient." Instead, a skilled artisan would understand the language "[a] method for treating an angiogenic eye disorder in a patient" in the context of the '338 patent to require effectively treating a patient's angiogenic eye condition.

B. "Tertiary Dose(s)"

41. Claims 1 and 14 requires that "tertiary dose(s)" are "administered at least 8 weeks after the immediately preceding dose." Ex. 1001 at 23:10-11.

42. It is my opinion that "tertiary dose(s)" means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

43. As of the filing date, and even today, the term "tertiary dose(s)" does not have a well-understood meaning to a skilled artisan in the fields of

ophthalmology or retina medicine outside the context of the '338 patent. In my experience, with which Dr. Albini agrees, the term "tertiary dose(s)" is not typically used by clinicians or the skilled artisan. Ex. 1002, ¶ 41.

44. Dr. Albini states that a skilled artisan would understand the term "tertiary dose(s)" as used in the claims of the '338 patent based solely on the following passage from the '338 patent specification:

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

Ex. 1001 at 3:31-45.

45. But in my view, the '338 patent specification provides more context for the meaning of the term "tertiary dose" than the isolated passage above. Indeed, the '338 patent specification explains that, at the time of patent filing in January 2011, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001 at 1:49-52. Nonetheless, the '338 patent recognized that there remained a need for less frequent dosing regimens that could maintain a high

degree of efficacy. *Id.* at 1: 55-59. The '338 patent successfully addressed this long-felt need:

> "The present inventors have ***surprisingly*** discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks."

Id. at 2:3-10 (emphases added).

46. The '338 patent specification makes clear that a key benefit of the claimed dosing regimens is that for "most of the course of treatment (*i.e.* the ***tertiary doses***)" patients may be treated less frequently as compared to therapies that existed in the art (i.e., monthly dosing). *Id.* at 2:15-22 (emphasis added). In my opinion, the disclosed dosing regimens were a significant advance over existing therapies because they enabled physicians, like myself, to treat patients using less frequent dosing, but to maintain a high degree of therapeutic efficacy.

47. I agree with Dr. Albini that the passage at column 3, lines 31-45 quoted above informs the temporal sequence of "initial dose," "secondary dose" and "tertiary dose(s)." I also agree that the "tertiary dose(s)" are third in the sequence of these doses but, in my opinion, this passage does not provide any guidance as to how to determine the appropriate magnitude of the "tertiary dose(s)." However, Patent

Owner's construction captures the full meaning of the term "tertiary dose(s)" in the context of the specification.

48. I also understand that Petitioner argues, and Dr. Albini agrees, that in the context of the '338 patent, "efficacy" "only requires that the patient exhibit a loss of fifteen or fewer letters on the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation." Pet. 21; Ex. 1002, ¶ 43. As I read the claims of the '338 patent, in view of the specification, this level of efficacy would not be sufficient for the dosing regimens claimed in the '338 patent. For example, if a patient achieved a letter gain after the initial and secondary doses and then declined after the tertiary dose(s) began, but nonetheless exhibited a loss of fewer than 15 letters during the tertiary dosing, I would not consider this level of efficacy to be sufficient for the dosing regimens claimed in the '338 patent. Rather, I understand "tertiary dose(s)" to require that the efficacy gain achieved from the initial and secondary doses are maintained after the initial and secondary doses. *See, e.g., supra* ¶ 45 (discussing passage in the specification that "[t]he present inventors have ***surprisingly*** discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered

to the patient at a frequency of about 2 to 4 weeks."). Thus, the claims as a whole require effective treatment.

49. Consequently, in my opinion, the term "tertiary dose(s)," when viewed from the perspective of a skilled artisan in the context of the specification, means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

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

Dated: August 13, 2021

Diana Do, MD

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Palo Alto, California

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Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies

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Purpose: To evaluate the impact of intravitreal aflibercept (EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY) versus laser on progression of diabetic retinopathy (DR) severity in Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME).

Design: Secondary and exploratory analyses of 2 phase 3, randomized, controlled studies.

Participants: All patients with a baseline Diabetic Retinopathy Severity Scale (DRSS) score based on fundus photograph (full analysis), patients who progressed to proliferative DR (PDR) (safety analysis) in VIVID-DME (n = 403) and VISTA-DME (n = 459), or both.

Methods: We randomized patients with diabetic macular edema (DME) to intravitreal aflibercept 2 mg every 4 weeks (2q4), intravitreal aflibercept 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit.

Main Outcome Measures: Proportions of patients with 2-step or more and 3-step or more improvements from baseline in DRSS score, who progressed to PDR, and who underwent panretinal photocoagulation (PRP).

Results: Among patients with an assessable baseline DRSS score, most showed moderately severe or severe nonproliferative DR. The proportions of patients treated with 2q4, 2q8, and laser with a 2-step or more improvement in DRSS score at week 100 were 29.3%, 32.6%, and 8.2%, respectively, in VIVID-DME and 37.0%, 37.1%, and 15.6%, respectively, in VISTA-DME; the proportions with a 3-step or more improvement in DRSS score were 7.3%, 2.3%, and 0%, respectively, and 22.7%, 19.9%, and 5.2%, respectively. Fewer patients in the 2q4 and 2q8 groups versus the laser group progressed to PDR at week 100 in VISTA-DME (1.5% and 2.2% vs. 5.3%) and VIVID-DME (3.2% and 2.0% vs. 12.3%). The proportions of patients who underwent PRP were 2.9%, 0.7%, and 4.5%, respectively, in VIVID-DME and 1.9%, 0.7%, and 5.2%, respectively, in VISTA-DME. The most frequent serious ocular adverse event at week 100 was cataract (pooled intravitreal aflibercept, 1.7% of patients; laser, 3.5% of patients).

Conclusions: These analyses demonstrate the benefit of intravitreal aflibercept over laser with respect to DR progression, suggesting a benefit on DME, and on underlying DR. *Ophthalmology Retina 2018;2:988-996 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

See Editorial on page 985.

Diabetic retinopathy (DR) is a progressive dysfunction of the retinal vasculature resulting from chronic hyperglycemia.[1] Diabetic retinopathy has been classified into 4 stages: mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). Typical management of mild and moderate NPDR involves observation and improved control of diabetes, whereas severe NPDR and PDR require referral to an ophthalmologist. Treatment options for DR in the absence of diabetic macular edema (DME) target only proliferative stages of DR.

Diabetic macular edema may occur at any point in the course of DR, although it is more frequent as the disease progresses. Most vision loss associated with DR is the result of DME.[2] The estimated global prevalence of DME currently is approximately 21 million,[3] and this is expected to increase with the rising diabetes prevalence; diabetes is projected to affect nearly 600 million people worldwide by 2035.[4]

Intravitreal anti–vascular endothelial growth factor (VEGF) agents (aflibercept [EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY] and ranibizumab) are superior to laser for the treatment of center-involved DME.[5–9] Intravitreal aflibercept showed similar sustainable visual acuity (VA) gains with dosing every other month compared with

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ranibizumab given monthly. More recently, the National Institutes of Health–funded Protocol T study conducted by the Diabetic Retinopathy Clinical Research Network compared intravitreal aflibercept, ranibizumab, and nonlicensed bevacizumab head to head.[10] At 12 months, VA gains achieved with intravitreal aflibercept, the study's primary end point, were statistically superior to those achieved with ranibizumab or bevacizumab, particularly in patients with baseline VA of 20/50 or worse.[10] After 2 years, the visual gains achieved with intravitreal aflibercept were statistically superior to those with bevacizumab, but not ranibizumab[11]; however, an area under the curve analysis showed that mean change in VA over 2 years was greater with intravitreal aflibercept than with bevacizumab or ranibizumab.[12]

Vascular endothelial growth factor inhibition has been shown not only to influence the course of DME positively, but also to have a positive impact on overall DR severity.[6,13,14] Herein we report on an unplanned retrospective analysis of the impact of intravitreal aflibercept treatment on changes in Diabetic Retinopathy Severity Scale (DRSS) scores, progression of DR to PDR in patients with DME, and use of panretinal photocoagulation (PRP) in the Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME) studies.

Methods

Design

Study design and methods have been published previously.[8,9] Key details are summarized here. Both VIVID-DME (clinicaltrials.gov identifier, NCT01331681) and VISTA-DME (clinicaltrials.gov identifier, NCT01363440) were phase 3, randomized, double-masked, active-controlled, 148-week trials comparing 2 dosing regimens of intravitreal aflibercept with laser for the treatment of DME. The studies were conducted at 127 sites in the Unites States, Europe, Japan, and Australia and in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation. All information presented in this study complies with the Health Insurance Portability and Accountability Act for United States sites. Institutional review board or ethics committee approval was obtained at each site before the studies commenced, and all patients provided written consent.

Participants

Adult patients with diabetes mellitus with central DME involvement (defined as retinal thickening involving the 1-mm central OCT subfield [central subfield thickness]) were included if best-corrected VA (BCVA) was between 73 and 24 letters (Snellen equivalent, 20/40–20/320) in the study eye. Only 1 eye per patient was included.

Randomization and Treatment

We randomized patients 1:1:1 to treatment with intravitreal aflibercept 2.0 mg every 4 weeks (2q4), intravitreal aflibercept 2.0 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit. Eyes in the 2q8 group received sham injections on nontreatment visits. From week 24 onward, additional active treatment (laser in the intravitreal aflibercept groups or intravitreal aflibercept in the laser group) was allowed if BCVA decreased because of disease reoccurrence or worsening based on prespecified criteria. Panretinal photocoagulation was allowed at any time at the investigator's discretion for PDR.

Outcomes

The primary efficacy end point in VIVID-DME and VISTA-DME was the BCVA change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores at week 52. Results for the primary end point of these studies are reported elsewhere.[8] Herein, we report the proportion of eyes with 2-step or more and 3-step or more improvement in DRSS score at weeks 52 and 100, the proportion of eyes in which PDR developed at weeks 52 and 100, and the proportion of eyes that underwent PRP at weeks 52 and 100. The 2-step or more improvement in DRSS score was a prespecified secondary end point at week 52 and an exploratory end point at week 100 for these studies.

We assessed central subfield thickening using spectral-domain OCT every 4 weeks, and performed fluorescein angiography and color fundus photography at baseline and weeks 24, 52, and 100. Masked graders evaluated images at independent reading centers. For VIVID-DME, readers at the Vienna Reading Center (Vienna, Austria) evaluated OCT images and fundus images. For VISTA-DME, clinicians at the Duke Reading Center (Durham, NC) assessed OCT images and clinicians at the Digital Angiography Reading Center (Great Neck, NY) evaluated fundus images. Although the 2 reading centers used similar methods, the differences in the proportions of ungradable images at baseline were the result of slightly different algorithms used by each center.

Patients were considered to have PDR if their baseline DRSS score was less than 61 and there was at least 1 postbaseline DRSS score of 61 or more. Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 and active PDR in the study eye were exclusion criteria for VIVID-DME and VISTA-DME. Approximately 5% of patients demonstrated PDR at baseline. It was agreed by the reading centers that DRSS level 60 (which indicates prior PRP) would not be used in the study, and therefore patients with prior PRP could still improve on the DRSS scale.

Statistical Analysis

Patients included in the efficacy analyses are those from the full analysis set (FAS) in both studies (VIVID-DME and VISTA-DME). This includes all randomized patients who received any study medication and underwent at least 1 baseline and 1 postbaseline assessment. We analyzed the FAS as randomized. In calculating the percentage of patients with a 2-step or more and 3-step or more improvement in DRSS score, the denominator for VIVID-DME was all patients in the FAS who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score; the denominator for VISTA-DME was all patients in the FAS. For patients missing a DRSS score at weeks 52 and 100, we imputed missing values using the last observation carried forward method, in which we used the last value before additional treatment for eyes that received additional treatment. The use of these different denominators is consistent with the health authority submission packages for the 2 studies. For the end point of PDR development, we excluded missing and ungradable entries for DRSS score from both studies.

We calculated results for all end points for each treatment group (2q4, 2q8, and laser) for VIVID-DME and VISTA-DME. Additionally, given the low number of cases of incident PDR, we integrated the populations from both studies and calculated the end points for 2 groups from that integrated population: a pooled intravitreal aflibercept group (2q4 and 2q8) and laser group. In the case of the integrated and pooled results, we based P values on the Fisher exact test without further adjusting for multiplicities. Patients included in safety analyses are from the safety population in both studies, which includes all randomized patients who received any study treatment.

Results

Changes from Baseline in Diabetic Retinopathy Severity Scale Scores

Of 862 patients in the FAS, 748 (86.8%) had a baseline DRSS score (Table 1). The proportions of DRSS images categorized as ungradable were 25%, 28.7%, and 25.2% for the Vienna Reading Center and 2.6%, 0.6%, and 2.0% for the Digital Angiography Reading Center for the laser, 2q4, and 2q8 groups, respectively.

A greater proportion of patients treated with intravitreal aflibercept (both 2q4 and 2q8) in both VIVID-DME and VISTA-DME demonstrated a 2-step or more improvement in DRSS scores at weeks 52 and 100 compared with laser-treated patients (Fig 1). When the data from the studies were integrated, the proportion of patients who showed a 2-step or more improvement was greater in the pooled intravitreal aflibercept group compared with the laser group (week 52: 31.1% vs. 12.0%, $P < 0.0001$; week 100: 34.9% vs. 13.0%, $P < 0.0001$; n = 578 and 287, respectively, for both time points).

The proportion of patients with a 3-step or more improvement in DRSS score at weeks 52 and 100 was greater among the groups treated with intravitreal aflibercept 2q4 and 2q8 than among those treated with laser (Fig 2). When the data from the studies were integrated, the proportion of patients who showed a 3-step or more improvement was greater in the pooled intravitreal aflibercept group compared with the laser group (week 52: 10.7% vs. 3.4%, $P = 0.0008$; week 100: 15.4% vs. 3.3%, $P < 0.0001$; n = 578 and 287, respectively, for both time points). Figure 3 shows a representative example of a fundus photograph from a patient treated with intravitreal aflibercept who experienced a 2-step or more improvement in DRSS score at week 52.

Progression to Proliferative Diabetic Retinopathy

A smaller proportion of patients in the intravitreal aflibercept 2q4 and 2q8 groups demonstrated PDR through weeks 52 and 100 compared with patients in the laser group (Fig 4). When the data from the studies were integrated, the proportion of patients in whom PDR developed was smaller in the pooled intravitreal aflibercept group compared with the laser group (week 52: 1.7% vs. 7.0%, $P = 0.0002$; week 100: 2.2% vs. 9.1%, $P \leq 0.0001$; n = 578 and 287, respectively, for both time points).

Finally, the proportion of patients treated with intravitreal aflibercept 2q4 and 2q8 versus laser who received PRP through weeks 52 and 100 was smaller than the proportion of laser-treated patients who received PRP (Fig 5). When we integrated the data from the studies, the proportion of patients who received PRP developed was smaller in the pooled intravitreal aflibercept group compared with the laser group (week 52: 0.9% vs. 3.5%, $P = 0.0099$; week 100: 1.6% vs. 4.9%, $P = 0.0064$; n = 578 and 287, respectively, for both time points). Not all cases of PDR led to

Table 1. Baseline Diabetic Retinopathy Severity Scale Scores in VIVID-DME and VISTA-DME

		VIVID-DME			VISTA-DME		
	Diabetic Retinopathy Severity Scale Score	*Laser (n = 132)*	*Intravitreal Aflibercept 2 mg Every 4 Weeks (n = 136)*	*Intravitreal Aflibercept 2 mg Every 8 Weeks after 5 Initial Monthly Doses (n = 135)*	*Laser (n = 154)*	*Intravitreal Aflibercept 2 mg Every 4 Weeks (n = 154)*	*Intravitreal Aflibercept 2 mg Every 8 Weeks after 5 Initial Monthly Doses (n = 151)*
None	10	0	0	0	1 (0.6)	4 (2.6)	4 (2.6)
Mild to moderate NPDR	20	1 (0.8)	0	0	3 (1.9)	5 (3.2)	3 (2.0)
	35	2 (1.5)	0	1 (0.7)	5 (3.2)	7 (4.5)	9 (6.0)
	43	36 (27.3)	31 (22.8)	28 (20.7)	60 (39.0)	49 (31.8)	52 (34.4)
Moderately severe/severe NPDR	47	24 (18.2)	18 (13.2)	27 (20.0)	26 (16.9)	26 (16.9)	32 (21.2)
	53	35 (26.5)	44 (32.4)	42 (31.1)	42 (27.3)	53 (34.4)	40 (26.5)
Mild/moderate/high-risk/ advanced PDR	61	1 (0.8)	2 (1.5)	2 (1.5)	1 (0.6)	1 (0.6)	2 (1.3)
	65	0	2 (1.5)	1 (0.7)	10 (6.5)	4 (2.6)	5 (3.3)
	71	0	0	0	1 (0.6)	4 (2.6)	1 (0.7)
	75	0	0	0	1 (0.6)	0	0
Cannot grade	90	33 (25)	39 (28.7)	34 (25.2)	4 (2.6)	1 (0.6)	3 (2.0)

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VISTA-DME = Intravitreal Aflibercept Injection in Vision Impairment due to DME; VIVID-DME = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema.
Full analysis set. Data are no. (%).

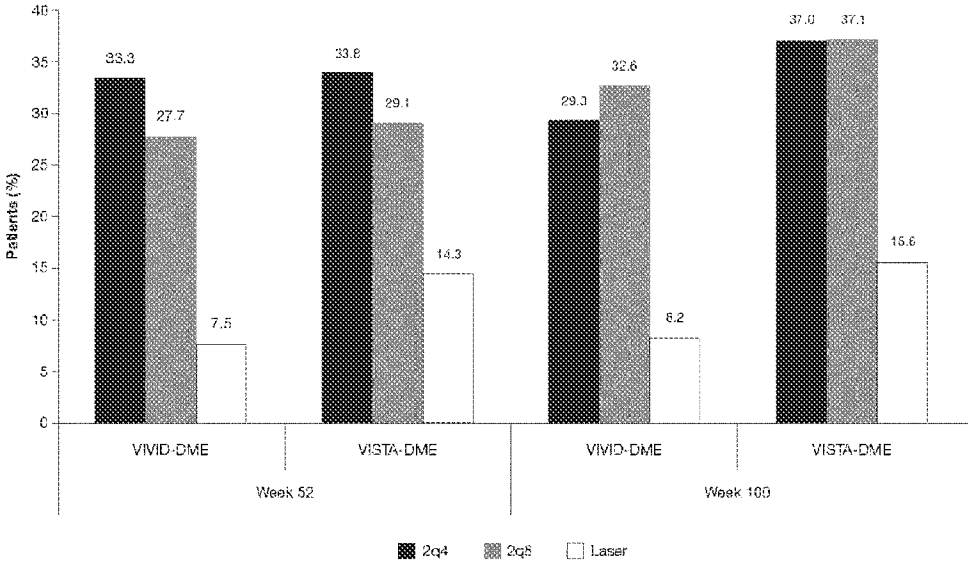

Figure 1. Bar graph showing the proportion of patients with 2-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. For analysis of DRSS, all patients in the full analysis set (FAS) who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score were included. VIVID-DME: laser, n = 132; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 154; 2q8, n = 151.

PRP; it is possible that PRP was administered at time points other than the DRSS reading time points, leading to the different proportions seen in Figures 4 and 5.

Safety

The incidence of adverse events related to the progression of DR was low. The proportions of patients who underwent vitrectomy in the laser, intravitreal aflibercept 2q4, and intravitreal aflibercept 2q8 treatment groups were 0%, 0.7%, and 0%, respectively, in VIVID-DME and 0.6%, 1.9%, and 0.7%, respectively, in VISTA-DME. The proportions of patients in the laser, intravitreal aflibercept 2q4, and intravitreal aflibercept 2q8 treatment groups in whom vitreous hemorrhage developed through week 100 were 4.5%, 2.9%, and 3.0%, respectively, in VIVID-DME and 9.1%, 6.5%, and 2.0%, respectively, in VISTA-DME.

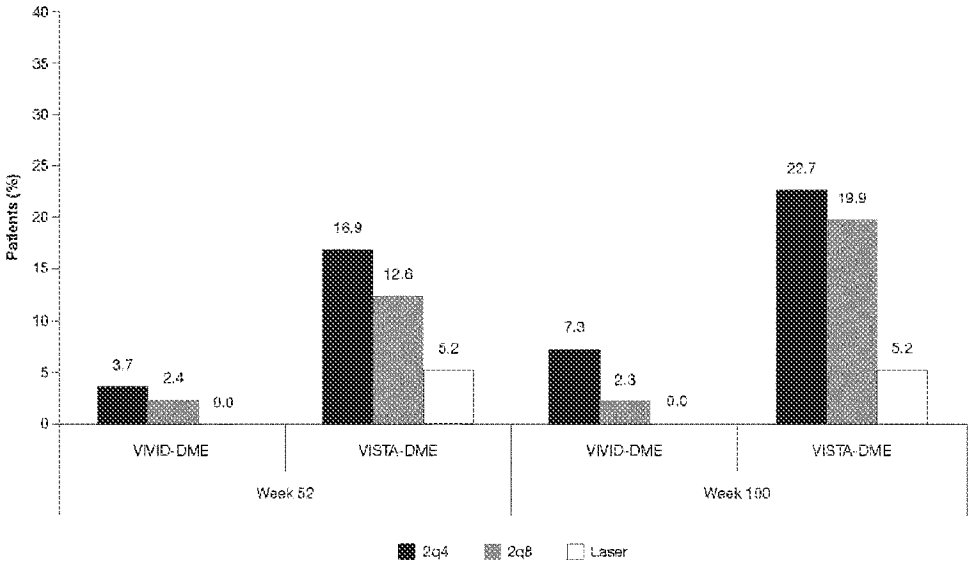

Figure 2. Bar graph showing the proportion of patients with 3-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. For analysis of DRSS, all patients in the full analysis set (FAS) who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score were included. VIVID-DME: laser, n = 132; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 154; 2q8, n = 151.

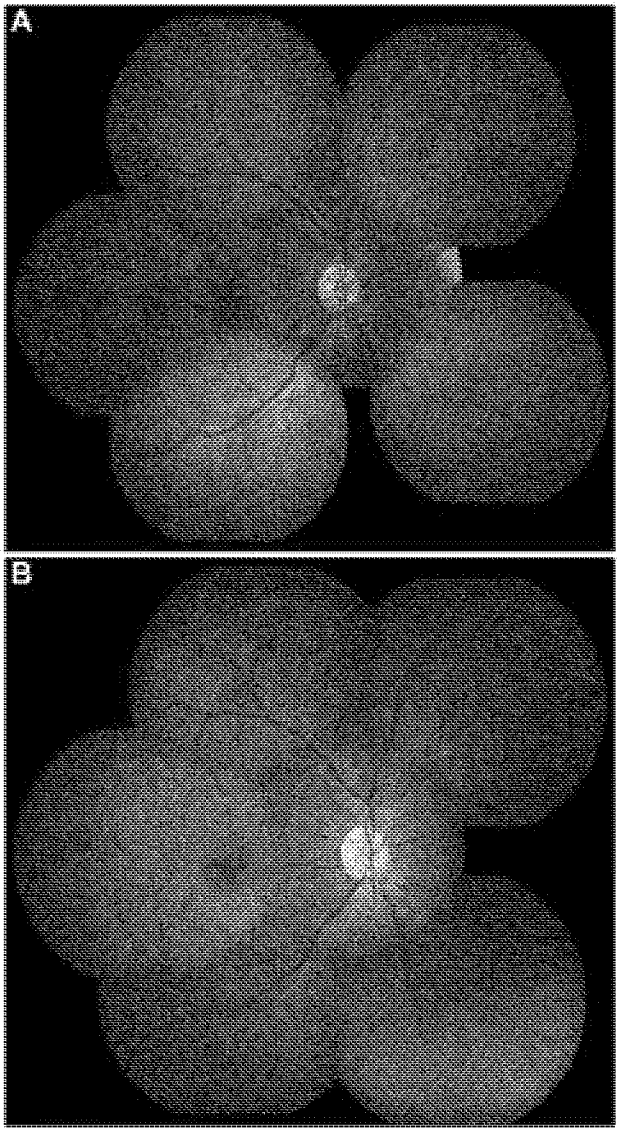

Figure 3. Representative examples of fundus photographs from an intravitreal aflibercept-treated patient from VIVID-DME who experienced a 2-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score (A) at baseline and (B) at week 52.

Discussion

These analyses evaluated the impact of intravitreal aflibercept on DR in patients with DME enrolled in the VIVID-DME and VISTA-DME trials. Compared with laser, the proportion of patients in the intravitreal aflibercept groups who achieved a 2-step or more and 3-step or more improvement in DRSS score was greater, and the proportion of patients in whom PDR developed, who were treated with PRP, or both was smaller. These results were seen in both the 2q4 and 2q8 treatment groups, suggesting that a reduced number of intravitreal aflibercept injections does not decrease the treatment benefit provided.

The Diabetic Retinopathy Clinical Research Network Protocol S study demonstrated that, in eyes with PDR, ranibizumab 0.5 mg administered as needed was noninferior to PRP with respect to BCVA outcomes at 2 years, and the cumulative benefit of ranibizumab over the study period was superior to PRP.[35] In the Clinical Efficacy of Intravitreal Aflibercept versus Panretinal Photocoagulation for Best Corrected Visual Acuity in Patients with Proliferative Diabetic Retinopathy at 52 weeks (CLARITY) study, intravitreal aflibercept administered as needed (after 3 initial monthly doses) was noninferior and superior to PRP in terms of mean change in BCVA at 52 weeks.[36] The Diabetic Anti-VEGF study compared ranibizumab 0.3-mg monotherapy with combination ranibizumab plus targeted retinal photocoagulation and found no differences between groups in visual improvement or decreases in central retinal thickness (Brown DM et al. Unpublished observations, 2015). These studies suggest a beneficial effect of anti-VEGF on the underlying diffuse DR in eyes with DME, which also was seen in the current analyses.

The VIVID-DME and VISTA-DME trials were the first anti-VEGF studies to examine the improvement of DR as a prespecified end point; however, progression of DR has been evaluated in other studies. The A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE) and A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE) studies found a trend similar to those seen in VIVID-DME and VISTA-DME, with a greater proportion of ranibizumab-treated patients experiencing a 2-step or more or 3-step or more improvement in DRSS score compared with sham-treated patients and a smaller proportion in whom PDR developed or who underwent PRP.[37] However, the results in RISE and RIDE were achieved with monthly injections of ranibizumab (median of 24 injections over 2 years),[8] whereas in the 2q8 group of VIVID-DME and VISTA-DME, the total number of injections received from baseline to week 100 was lower (mean, 13.5 injections in VISTA and 13.6 injections in VIVID over 2 years[9]). Additionally, the distribution of baseline DRSS scores was different in RISE and RIDE compared with VIVID-DME and VISTA-DME. In RISE and RIDE, the distribution of patients with mild to moderate NPDR, moderately severe to severe NPDR, and PDR was roughly equal (approximately one third of patients in each group).[37] In VIVID-DME and VISTA-DME, nearly half of patients demonstrated moderately severe to severe NPDR at baseline, and less than 10% demonstrated PDR (Table 1).

The Diabetic Retinopathy Clinical Research Network conducted an exploratory analysis of the Protocol I study to evaluate the effects of intravitreal ranibizumab or triamcinolone on the progression of DR, which was defined as (1) worsening from no PDR to PDR, (2) worsening of 2 or more severity levels on reading center assessment of fundus photographs in eyes without PDR at baseline, (3) having PRP, (4) having vitreous hemorrhage, or (5) requiring vitrectomy for treatment of PDR. Intravitreal ranibizumab was associated with a reduced risk of DR worsening in eyes with

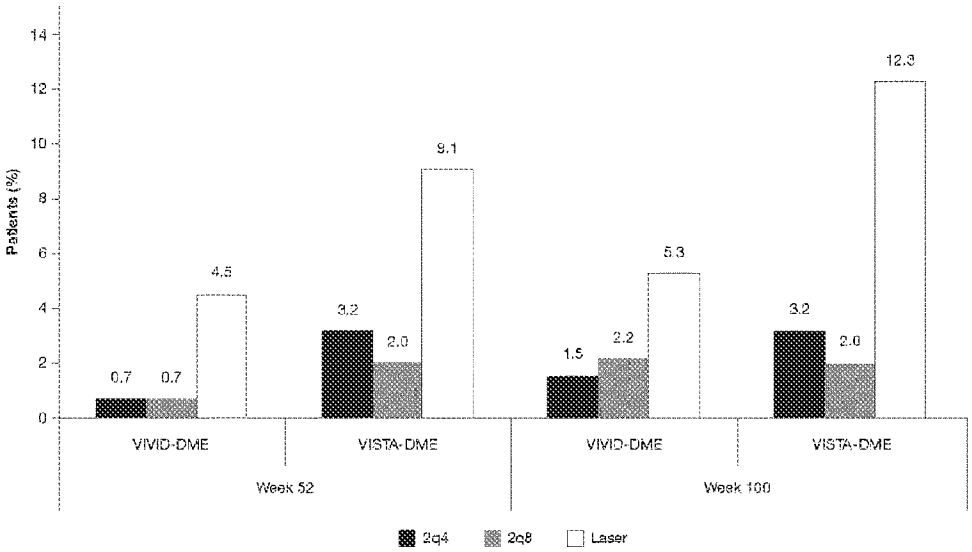

Figure 4. Bar graph showing the proportion of patients in whom proliferative diabetic retinopathy (PDR) developed, safety analysis set. For both studies, PDR development was defined as patients with baseline Diabetic Retinopathy Severity Scale (DRSS) value of less than 61 and at least 1 postbaseline DRSS value of 61 or more. VIVID-DME: laser, n = 133; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 155; 2q8, n = 152.

or without PDR, and intravitreal triamcinolone was associated with a reduced risk of PDR worsening.[18]

A post hoc analysis of the Protocol T study evaluated the proportion of patients with DR improvement at 1 and 2 years and the cumulative probabilities for DR worsening through 2 years without adjustment for multiple outcomes. In eyes with NPDR at baseline, anti-VEGF treatment resulted in improvement in DR severity for 22.1% to 37.7% at year 1 and 22.1% to 31.0% at year 2; less improvement was observed with bevacizumab compared with intravitreal aflibercept or ranibizumab. Among eyes with PDR at baseline, intravitreal aflibercept was associated with more DR improvement at 1 and 2 years. Use of all 3 anti-VEGF agents was associated with low rates of DR worsening.[14]

In the ETDRS, 1 eye of each patient was assigned to early photocoagulation, whereas the other was assigned to

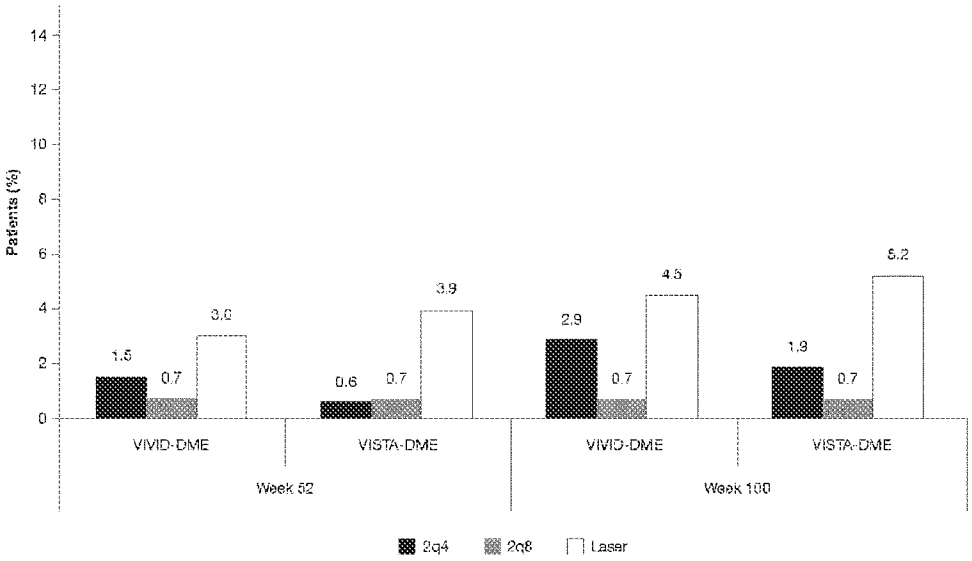

Figure 5. Bar graph showing the proportion of patients who underwent panretinal laser photocoagulation, safety analysis set. VIVID-DME: laser, n = 133; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 155; 2q8, n = 152.

deferred photocoagulation, allowing observation of the natural course of DR in the initially untreated eye. The proportions of eyes with progression to PDR were 22.8%, 40.2%, and 54.7%, at 1, 3, and 5 years of follow-up, respectively.[19] These proportions are substantially higher than the proportions of patients in whom PDR developed, who underwent PRP, or both in any of the treatment groups of VIVID-DME and VISTA-DME. The lower rates seen in the current studies may be the result of temporal improvements in glycemic control made possible by advances in diabetes treatment over the last 25 years, shown to reduce progression of DR.[20–24] Mean baseline hemoglobin A1c levels for patients in VIVID-DME and VISTA-DME ranged from 7.6% to 7.9% and did not change over the course of the study; in contrast, 42.0% of patients enrolled in the ETDRS before 1983 had a baseline hemoglobin A1c of 10% or more.[25]

The current analysis has some limitations. The relative infrequency of DRSS measurements (at baseline, weeks 24, 52, 72 [VISTA-DME] or 76 [VIVID-DME], and 100) means that it is possible that there are patients in any treatment group who did progress to PDR, but that this resolved spontaneously during continued treatment and was not captured. Additionally, investigators administered PRP at their discretion, a clinical decision that likely was driven by multiple factors. There was no specific guidance indicating when PRP should be performed, and therefore some investigators may have chosen to wait for high-risk PDR to develop. Others may have deferred PRP because of the expectation of a positive treatment effect on the condition. Finally, images for the 2 studies were graded by 2 different reading centers. The reading centers used different criteria to grade images; however, both approaches are considered valid per the ETDRS DRSS protocol. The overall similarity of the results between the 2 studies suggests that the different grading criteria did not impact the outcomes.

In conclusion, these analyses through week 100 demonstrated the benefits of intravitreal aflibercept over laser in terms of DR progression, improvement, and outcomes, suggesting that intravitreal aflibercept has a beneficial impact not only on localized DME, but also on the underlying DR.

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Footnotes and Financial Disclosures

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No animal subjects were used in this study.

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Analysis and interpretation: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown, Katz, Berliner, Vitti, Zeitz, Metzig, Lu, Holz

Data collection: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown

Obtained funding: N/A

Overall responsibility: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown, Katz, Berliner, Vitti, Zeitz, Metzig, Lu

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAS** = full analysis set; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **RIDE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VISTA-DME** = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; **VIVID-DME** = Intravitreal Aflibercept Injection in Vision Impairment due to DME; **2q4** = 2 mg every 4 weeks; **2q8** = 2 mg every 8 weeks after 5 initial monthly doses.

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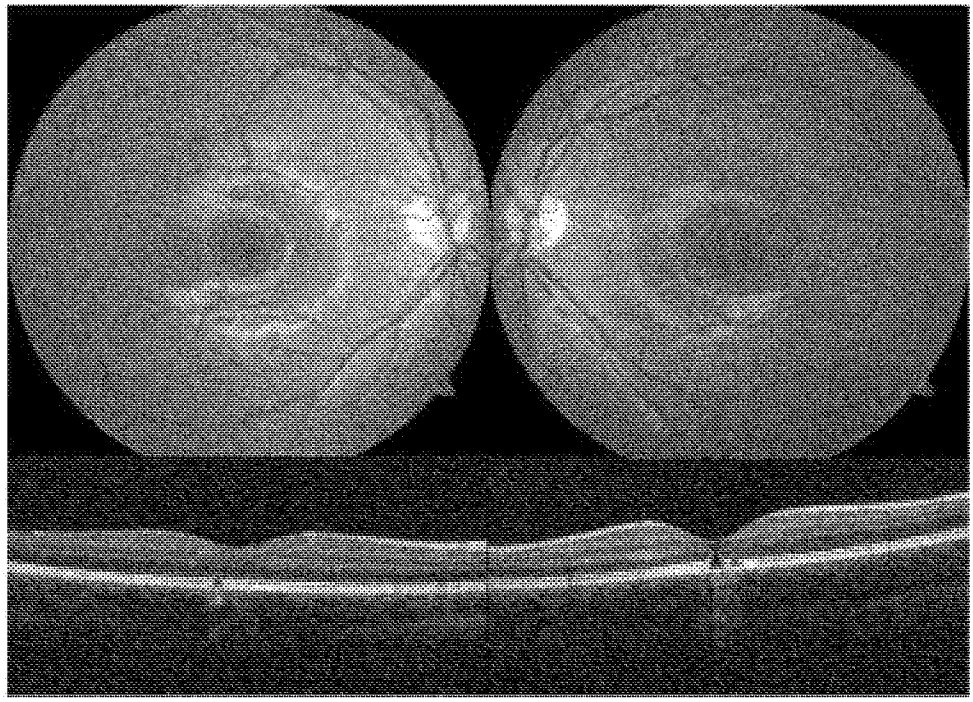
Pictures & Perspectives



Laser Pointer Maculopathy

An 11-year old Caucasian boy was referred for loss of vision for 1 year concerning for inherited retinal dystrophy. Best-corrected visual acuity was 20/30 in the right eye and 20/80 in the left. No family history of early vision loss was noted. Anterior segment examination was unremarkable. Dilated fundus examination showed irregular areas of foveal atrophy in both eyes. OCT shows a focal, well-circumscribed area of photoreceptor loss subfoveally in the left eye and parafoveally in the right eye. Upon further questioning, he admits that before noticing the vision changes a friend had shined a laser pointer in his eyes for a prolonged period of time.

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Prevention of Experimental Choroidal Neovascularization and Resolution of Active Lesions by VEGF Trap in Nonhuman Primates

T. Michael Nork, MD, MS; Richard R. Dubielzig, DVM; Brian J. Christian, PhD; Paul E. Miller, DVM; Jacqueline M. Miller, BS; Jingtai Cao, MD, PhD; Edward P. Zimmer, PhD; Stanley J. Wiegand, PhD

Objective: To evaluate the efficacy of systemic and intravitreous administration of VEGF Trap (aflibercept) in a nonhuman primate model of choroidal neovascularization (CNV).

Methods: VEGF Trap treatment on laser-induced CNV was evaluated in 48 adult cynomolgus monkeys. In the prevention arms of the study, VEGF Trap was administered by intravenous injection (3 or 10 mg/kg weekly) or intravitreous injection (50, 250, or 500 µg/eye every 2 weeks) beginning before laser injury. In the treatment arm, a single intravitreous injection (500 µg) was given 2 weeks following laser injury. Laser-induced lesions were scored from grade 1 (no hyperfluorescence) to grade 4 (clinically relevant leakage). Representative lesions were evaluated histologically.

Results: Grade 4 leakage developed at 32.4% and 45.4% of the laser sites in animals receiving intravitreous or intravenous administration of placebo at 2 weeks following laser injury, respectively. In contrast, the development of grade 4 lesions was completely or nearly completely prevented in all groups receiving intravenous or intravitreous injections of VEGF Trap. A single intravitreous injection of VEGF Trap (500 µg) administered following the development of CNV reduced the frequency of grade 4 lesions from 44.4% to 0% within 14 days of treatment. Intravitreous VEGF Trap was well tolerated with either no or only mild ocular inflammation. Histological evaluation showed decreased scores for morphologic features of tissue proliferation in the VEGF Trap prevention groups.

Conclusions: VEGF Trap prevented the development of clinically relevant CNV leakage when administered at the lowest doses tested. Moreover, a single intravitreous injection induced inhibition of active CNV leakage.

Clinical Relevance: The animal model used in this study has an established track record as a predictor of pharmacologic efficacy of antineovascular drugs in humans having the neovascular, or wet, form of age-related macular degeneration.

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AGE-RELATED MACULAR DEgeneration (AMD) is a leading cause of blindness whose incidence is likely to increase as the population ages.[1] The great majority of individuals with AMD have the dry form, which is characterized by atrophic degeneration of the retinal pigment epithelium with secondary (and often gradual) damage to the photoreceptors. However, 80% to 90% of patients with AMD who develop severe vision loss have the wet (neovascular) form,[2] which occurs when abnormal new blood vessels originating from the choroid grow through the Bruch membrane into the subretinal or intraretinal space. This choroidal neovascularization (CNV) was formerly treated with thermal laser photocoagulation according to protocols developed as part of the Macular Photocoagulation Study and related subsequent studies.[3-8] Although the treatment was effective at slowing the progression of the disease, it seldom resulted in improved vision because the thermal laser also irreversibly damaged the overlying retina. The patients were often left with central scotomas from the treatment itself. Since then, drugs such as pegaptanib sodium (Macugen) and ranibizumab (Lucentis) have been developed for human use; these work by inhibiting vascular endothelial growth factor (VEGF).

VEGF Trap is a potent VEGF inhibitor comprising ligand-binding portions of human VEGF receptor 1 (VEGFR1) and VEGFR2 fused to the Fc segment of human IgG1 (**Figure 1**).[9] VEGF Trap binds and neutralizes multiple isoforms of

VEGF-A (dissociation constant of approximately 1pM) as well as the related angiogenic factor placental growth factor (PlGF) (dissociation constant of approximately 40pM). An intravenous formulation of VEGF Trap, generically known as aflibercept, is being developed for oncology; this formulation is hyperosmotic and diluted prior to intravenous infusion. VEGF Trap-Eye, known generically as aflibercept ophthalmic solution, is an isoosmotic, ultrapurified formulation of VEGF Trap for intravitreous injection. Phase 3 studies of VEGF Trap-Eye in patients with neovascular AMD and retinal vein occlusion are currently in progress.

The purposes of this study were to evaluate the efficacy of systemic and intravitreous administration of VEGF Trap in a primate model of CNV and to evaluate histological changes associated with the angiographic improvements observed. This study was completed prior to initiating the human clinical trial program for VEGF Trap-Eye.

METHODS

LASER INDUCTION OF CNV

The effect of VEGF Trap treatment on laser-induced CNV was evaluated in cynomolgus monkeys (1.8-2.7 kg at initiation of dosing) using a modification[10] of a model of CNV developed by Ryan[11] and Ohkuma and Ryan.[12] All of the experimental methods and techniques adhered to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by our institutional animal care and use committee. Animals were anesthetized with ketamine hydrochloride and xylazine hydrochloride. A 532-nm diode laser (OcuLight GL; Iridex Corp, Mountain View, California) with a table-mounted slitlamp adapter was used to create small (75-μm diameter), intense laser spots of 0.1-second duration that were applied to 9 areas of the macula of each eye. Initially, the power setting was 500 mW for all spots except the one just temporal to the fovea, which was treated with 400 mW. If no hemorrhage occurred at a given spot, a second spot was placed adjacent to it using a laser intensity of 150 mW greater than the initial burn. The development of active CNV lesions was assessed by fluorescein angiography (FA), once before injury and 15, 20, and 29 days after laser injury. The CNV lesions were graded by a masked observer (T.M.N.) using the following scale: grade 1, no hyperfluorescence; grade 2, hyperfluorescence, without leakage; grade 3, hyperfluorescence early or midtransit, and late leakage; and grade 4, bright hyperfluorescence early or midtransit, with late leakage extending beyond the borders of the laser spot.

TREATMENT PARADIGMS

In the prevention studies, VEGF Trap was administered by intravenous injection (3 or 10 mg/kg of body weight weekly) or intravitreous injection (50, 250, or 500 μg/eye every 2 weeks) beginning approximately 1 week before laser injury. For intravitreous injection, VEGF Trap was formulated in 10mM sodium phosphate, 135mM sodium chloride, and 0.1% polyethylene glycol 3350 (pH 6.25) and injected through a 30-gauge sterile needle in a volume of 50 μL (500 or 50 μg) using a 1-mL tuberculin syringe or 25 μL (250 μg) using a 0.3-mL syringe. VEGF Trap for intravenous injection was formulated in 5mM sodium phosphate, 5mM sodium citrate, 100mM sodium chloride, 20% sucrose, and 0.1% polysorbate 20 (pH 6.0) and infused in a volume of 4 to 5 mL/kg of body weight over 30 minutes. Control animals received weekly intravenous infusions or biweekly intravitreous injections (50 μL) of placebo comprising the appropriate vehicle solutions according to the same schedule as for corresponding VEGF Trap–treated groups.

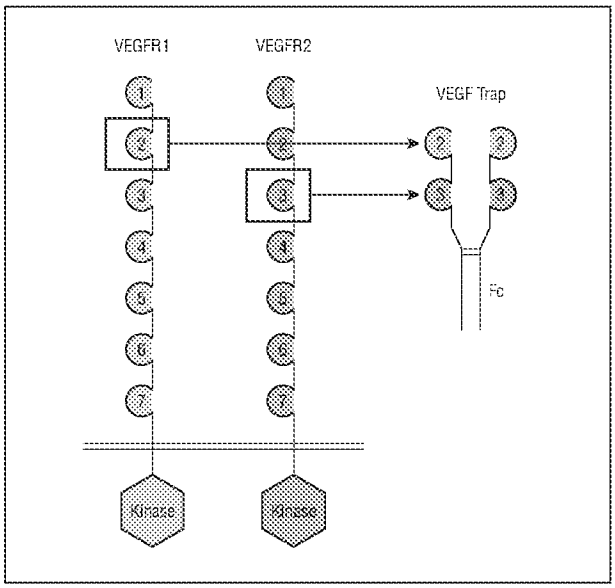

Figure 1. VEGF Trap is a fusion protein comprising the ligand-binding domains 2 and 3 of human vascular endothelial growth factor receptors 1 and 2 (VEGFR1 and VEGFR2), respectively, attached to the Fc portion of human IgG1. Recombinant VEGF Trap is produced in Chinese hamster ovary cells, has a protein molecular weight of 97 kDa, and is approximately 15% glycosylated to yield a total molecular weight of 115 kDa.

In the treatment study, a single intravitreous injection of VEGF Trap (500 μg) was given 15 days following laser injury, at which time active CNV had already formed. Each of the experimental and control groups comprised 6 animals, including 3 males and 3 females; both eyes were treated identically (**Table 1**).

INTRAVITREOUS INJECTIONS

Animals were anesthetized with ketamine and xylazine, and the eyes were instilled with 0.5% proparacaine hydrochloride, cleaned with 2.5% povidone-iodine, and rinsed with sterile saline. Immediately following each injection, a single topical dose of tobramycin and dexamethasone (Tobradex) ointment was applied to the eye. No systemic antibiotics were used. The left and right eyes of each animal received the same dose of either VEGF Trap or placebo (as opposed to a study design that used the fellow eye as the control) to eliminate the possibility of a systemic effect on the control eye.

OPHTHALMIC EXAMINATIONS

Daily cage-side observations were performed on all animals to monitor for clinical signs of poor health, including any ocular abnormalities. Animals also underwent clinical ophthalmic examinations before the initiation of treatment and on postlaser days 7, 21, and 32 (intravitreous prevention groups) and days 9, 23, and 33 (intravenous prevention groups and intravitreous treatment group, excluding day 9). The anterior portion of each eye was viewed using a handheld slitlamp biomicroscope, and the ocular fundus was viewed with an indirect ophthalmoscope. Intraocular pressure was monitored. Fundus photographs were taken on the day of laser treatment (following laser injury) and approximately 4 weeks later, preceding the final FA.

Table 1. Group Designation and Dose Levels

Group[a]	Animals, No. Male	Animals, No. Female	Dose Volume	Dose Concentration, mg/mL
Intravenous prevention				
Placebo	3	3	4.78 mL/kg	0
3 mg/kg/dose	3	3	4.35 mL/kg	0.69
10 mg/kg/dose	3	3	4.78 mL/kg	2.09
Intravitreous prevention				
Placebo	3	3	0.05 mL/eye	0
50 µg/eye/dose	3	3	0.05 mL/eye	1
250 µg/eye/dose	3	3	0.025 mL/eye	10
500 µg/eye/dose	3	3	0.05 mL/eye	10
Intravitreous treatment				
Single dose of 500 µg/eye	3	3	0.05 mL/eye	10

[a] Animals in the 2 control groups (intravenous and intravitreous) were administered a placebo vehicle following the same regimens as treated animals in the intravenous and intravitreous VEGF Trap treatment arms. In the prevention studies, intravenous doses were administered weekly for a total of 6 doses, and intravitreous doses were administered every other week for a total of 3 doses, beginning approximately 1 week before laser injury. In the treatment study, animals received a single dose of VEGF Trap following the establishment of active grade 4 lesions, 15 days following laser injury. See Figure 2 for the dosing schedule.

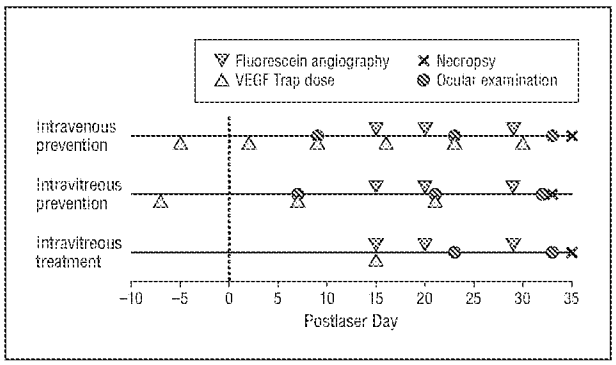

Figure 2. Timeline for dosing, ocular examinations, and fluorescein angiography relative to laser photocoagulation.

Anterior chamber and vitreous cell scores were determined for right and left eyes using a slitlamp biomicroscope as follows: a score of 0 indicates no cells observed; a score of 0.5+, 1 to 5 cells per single field of focused beam; a score of 1+, 5 to 25 cells per single field of focused beam; a score of 2+, 25 to 50 cells per single field of focused beam; a score of 3+, 50 to 100 cells per single field of focused beam; and a score of 4+, more than 100 cells per single field of focused beam. Scores from both eyes were averaged per animal. Means and standard deviations are based on 6 animals per group. **Figure 2** shows the timing of dosing, FA, ophthalmic examinations, and necropsy relative to the day of laser treatment for each of the 3 treatment arms.

STATISTICAL ANALYSIS OF LASER LESION GRADES

For each of the 3 postlaser angiography intervals (days 15, 20, and 29), the proportions of grade 4 counts were dichotomized to 1 and 0 and the Cochran-Armitage trend test was applied to the intravenous prevention and intravitreous prevention groups separately. Fisher exact tests were also conducted for group comparisons between treated groups and the control group.

For the intravitreous treatment group and the intravitreous prevention placebo group, data from day 15 were treated as baseline data and were subtracted from the data on days 20 and 29. The difference was then analyzed for days 20 and 29 separately using Wilcoxon signed rank test.

All test results are exact because of the small sample sizes. All statistical tests were conducted at the 5% level.

HISTOLOGICAL ASSESSMENT OF CNV LESIONS

Animals were killed on postlaser day 33 (intravitreous prevention groups) or day 35 (intravenous prevention groups and intravitreous treatment group) and the upper body was perfused through the aorta (descending clamped) with half-strength Karnovsky fixative. The eyes were removed, post-fixed for 2 to 3 days in half-strength Karnovsky fixative, and then stored in formalin until processed.

One eye from each animal in the intravitreous placebo, VEGF Trap (500 µg) prevention, and VEGF Trap treatment groups was selected for histopathological evaluation. The selected eyes were representative and comprised approximately half of the grade 4 lesions for each of the groups. Strips of tissue containing 1 or 2 lesion sites were embedded in plastic. Sections 2 µm thick were taken at 30-µm steps through the middle of each lesion. The sections were stained with toluidine blue, and the sample with the most robust lesion was designated as the central cut. This section was then evaluated by an observer (R.R.D.) masked to the treatment condition.

A tissue proliferation score was calculated for each lesion based on 3 criteria: the size of the spindle cell proliferative lesion, the extent of new blood vessel proliferation in the subretinal space, and the elevation of the retina above the choriocapillaris (**Figure 3**). Each measure was graded from 0 to 3, with 0 indicating not present. The total tissue proliferation score comprises the sum of each of the described measures for each laser lesion site.

RESULTS

INFLAMMATORY RESPONSE

Intravitreous administration of the VEGF Trap placebo control article was well tolerated, with 0.5+ vitreous cells seen in 1 of 6 animals in this group. No anterior chamber cells were detected at the designated examination times in animals receiving intravitreous injections of placebo (**Table 2**).

Intravitreous administration of the VEGF Trap test material at all dose levels resulted in no (0) or mild (0.5+ to 1+) inflammatory cell scores in the anterior chamber or vitreous. During the course of the study, trace (0.5+) levels of anterior chamber cells were seen in 4 of 6 animals in the mid-dose group (250 µg/eye/dose) and 3 of 6 animals in the high-dose group (500 µg/eye/dose) in the multiple (biweekly) intravitreous dose prevention experiment and in 1 of 6 animals in the single intravitreous dose treatment study (500 µg/eye following CNV formation). Vitreous cell scores were also mild (0.5+ to 1+) in all of the groups that underwent intravitreous injection of VEGF Trap, but vitreous cells were more frequent and detected in all animals in these groups at some time during the study. This finding was not unexpected, because inflammatory cells are much slower to enter and clear from the more viscous vitreous gel than the aqueous humor. These results are summarized in Table 2. At no time or dose did the mean cell inflammatory score exceed 1+ in any eye. Ocular examinations were performed approximately 2 weeks following injections in the intravitreous prevention study, so early transient inflammation may have been missed. However, the animals in the intravitreous treatment group were examined 8 days after injection and only mild inflammation was observed (on study day 23) (Table 2). No animals showed gross evidence of ocular or systemic toxic effects based on daily cage-side inspections. There were no significant effects on intraocular pressure beyond a transient elevation in all groups immediately following intravitreous injection.

Intravenous administration of VEGF Trap placebo or VEGF Trap at a low or high dose produced no detectable anterior chamber or vitreous cells.

No evidence of a retinal inflammatory response (eg, perivascular sheathing, retinal thickening, optic nerve swelling, or retinal vascular leakage) was found on color fundus photography or FA in any of the animals.

FLUORESCEIN ANGIOGRAMS

Of the 4 grades assigned to the laser treatment spots, grade 4 (bright hyperfluorescence early or midtransit, with late leakage extending beyond the borders of the laser spot) corresponds to clinically significant leakage. Grade 4 lesions are thought to reflect the presence of new choroidal vessels that either have grown beyond the laser treatment spot or are leaking so intensely that the fluorescein dye has spread markedly away from the vessels. The results with respect to grade 4 leakage for all groups are shown in **Table 3**. The average number of grade 4 lesions in the intravitreous placebo group ranged from 26.9% to 32.4% during the times evaluated (postlaser days 15, 20, and 29), while 45.4% to 50.0% of the laser treatment areas show grade 4 leakage in the intravenous placebo group. The mean percentage of grade 4 lesions in the control groups was similar to that which has been reported by others using this animal model of CNV.[10,11,13] By contrast, all of the VEGF Trap prevention groups showed marked reduction or complete absence of grade 4 lesions, irrespective of dose (**Figure 4** and **Figure 5**). **Table 4** shows the distribution of all lesion grades on day 29 for the prevention groups.

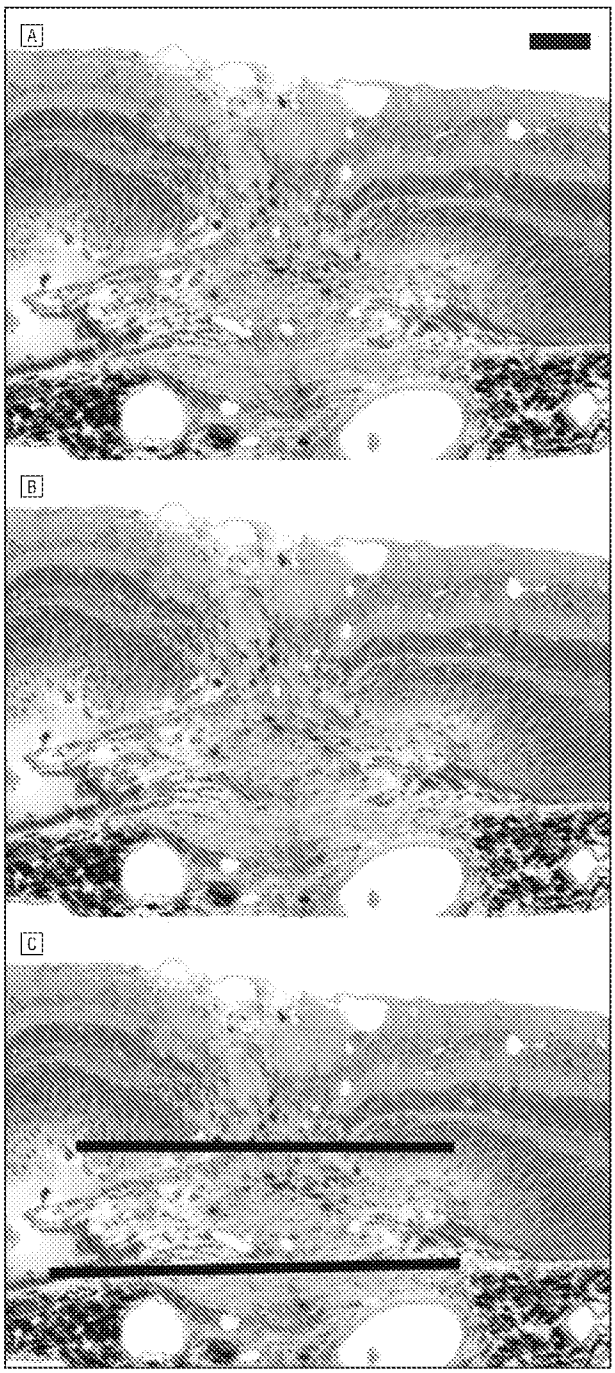

Figure 3. Semiquantitative scoring of lesions (glycol methacrylate sections stained with toluidine blue; scale bar=250 µm). A, Choroidal fibroplasia (pink). A score of 0 indicates none; 1, small, focal; 2, once the retinal thickness across; and 3, twice the retinal thickness across. B, Choroidal neovascularization (red). A score of 0 indicates none; 1, single small focus; 2, one tuft of vessels; and 3, multiple vessels extending once or twice the retinal thickness. C, Retinal elevation (distance between the lines). A score of 0 indicates none; 1, less than 0.2 times the retinal thickness; 2, less than 0.4 times the retinal thickness; and 3, less than 0.6 times the retinal thickness.

In the VEGF Trap treatment group (single intravitreous injection of VEGF Trap administered on postlaser day 15), 44.4% of laser treatment spots exhibited grade 4 leakage on day 15, similar to the percentage of grade 4 spots in the 2 placebo control groups. However, by postlaser day 20 (5 days following intravitreous administration of VEGF Trap), only 1.9% of the spots were grade

Table 2. Inflammatory Response[a]

Group	Score, Mean (SD)[b]					
	Anterior Chamber Cells			Vitreous Cells		
Intravenous prevention	Day 9	Day 23	Day 33	Day 9	Day 23	Day 33
Placebo	0	0	0	0	0	0
3 mg/kg/dose	0	0	0	0	0	0
10 mg/kg/dose	0	0	0	0	0	0
Intravitreous prevention	Day 7	Day 21	Day 32	Day 7	Day 21	Day 32
Placebo	0	0	0	0.08 (0.2)	0.04 (0.1)	0.04 (0.1)
50 µg/eye/dose	0	0	0	0.71 (0.4)	0.42 (0.3)	0.46 (0.3)
250 µg/eye/dose	0.13 (0.2)	0.04 (0.1)	0.08 (0.1)	0.63 (0.2)	0.33 (0.4)	0.50 (0.3)
500 µg/eye/dose	0	0.17 (0.2)	0.17 (0.3)	0.88 (0.1)	0.67 (0.3)	0.63 (0.4)
Intravitreous treatment		Day 23	Day 33		Day 23	Day 33
Single dose of 500 µg/eye		0.08 (0.2)	0		0.71 (0.4)	0.50 (0.2)

[a] The days indicate the days following laser treatment.

[b] Numerical scoring from 0 to 4 based on the number of cells observed per single field of focused slitlamp beam: a score of 0.5 indicates 1 to 5 cells; a score of 1, 5 to 25 cells; a score of 2, 25 to 50 cells; a score of 3, 50 to 100 cells; and a score of 4, more than 100 cells. Scores from both eyes were averaged per animal, and the means and standard deviations are based on 6 animals per group. Anterior chamber or vitreous cells were not observed before dosing in any group.

Table 3. Mean Percentages of Grade 4 Lesions by Group

Group	Grade 4 Lesions, Mean %[a]		
	Day 15	Day 20	Day 29
Intravenous prevention[b]			
Placebo	45.4	50.0	45.4
3 mg/kg/dose	0[c]	0[c]	0.9[d]
10 mg/kg/dose	0[c]	0[c]	0[c]
Intravitreous prevention[e]			
Placebo	32.4	31.5	26.9
50 µg/eye/dose	0[c]	0.9[d]	0.9[d]
250 µg/eye/dose	0[c]	0[c]	0[c]
500 µg/eye/dose	0[c]	0[c]	5.6[d]
Intravitreous treatment			
Single dose of 500 µg/eye	44.4	1.9[f]	0[g]

[a] Mean percentages of grade 4 lesions by treatment group are shown across fluorescein angiography intervals (postlaser days).

[b] *P* values for trend test for the intravenous prevention days 15, 20, and 29 were <.001, <.001, and .002, respectively (decreasing trend).

[c] Significant difference (1-sided $P < .008$) of the treatment group (intravenous prevention or intravitreous prevention) from the relevant control group using Fisher exact test.

[d] Significant difference (1-sided $P < .04$) of the treatment group (intravenous prevention or intravitreous prevention) from the relevant control group using Fisher exact test.

[e] *P* values for trend test for the intravitreous prevention days 15, 20, and 29 were < 001, < 001, and .008, respectively (decreasing trend).

[f] Wilcoxon signed rank test for comparison between the intravitreous prevention placebo group and intravitreous treatment group showed a significant decrease in grade 4 lesions on day 20 (1-sided $P < .01$).

[g] Wilcoxon signed rank test for comparison between the intravitreous prevention placebo group and intravitreous treatment group showed a significant decrease in grade 4 lesions on day 29 (1-sided $P < .003$).

4; no spots were grade 4 at day 29 (Table 3, **Figure 6**, and **Figure 7**). When all lesion grades were compared, there was a marked shift from mostly grades 4 and 3 in the day 15 (pretreatment) angiograms to mostly grades 2 and 1 in the day 29 angiograms (**Figure 8**).

RETINAL HISTOLOGICAL EVALUATION

Consonant with the FA findings, histological evaluation revealed that intravitreous administration of VEGF Trap reduced proliferative responses of the retina to laser injury, particularly neovascular proliferation.

When VEGF Trap administration was begun prior to laser injury (prevention), choroidal fibroplasia and retinal elevation scores as well as CNV scores were all significantly lower in VEGF Trap–treated animals relative to placebo controls (**Table 5** and **Figure 9**). When a single injection of VEGF Trap was given after grade 4 lesions had developed, there was also a trend toward decreased CNV, but mean scores for fibroplasia and retinal elevation were not significantly different from controls (Table 5 and **Figure 10**).

COMMENT

BACKGROUND

Important advances were made in the treatment of AMD by the application of drugs that act to destroy and/or prevent formation of the new blood vessels. The first of these to be approved for human use was photodynamic therapy using the photosensitizing dye verteporfin (Visudyne; Novartis, Basel, Switzerland) administered intravenously followed by exposure of the CNV to 689-nm low-energy laser. Photodynamic therapy greatly reduced direct retinal damage from prior thermal laser therapy. However, there were problems with recurrence, and patients continued to have a decline in vision over time.[14]

Following the development of photodynamic therapy, a new family of drugs that act to inhibit the cytokine VEGF-A was developed. VEGF-A has been implicated as a causal factor in the development of the wet form of AMD as well as other ocular vascular diseases characterized by pathological neovascularization and vascular leak and/or edema. A number of strategies are being developed to inhibit VEGF-A signaling in these conditions, including application of antibodies to VEGF-A or the VEGF receptors, VEGF-binding aptamers, and small interfering RNAs and treatment with kinase inhibitors. The first of these

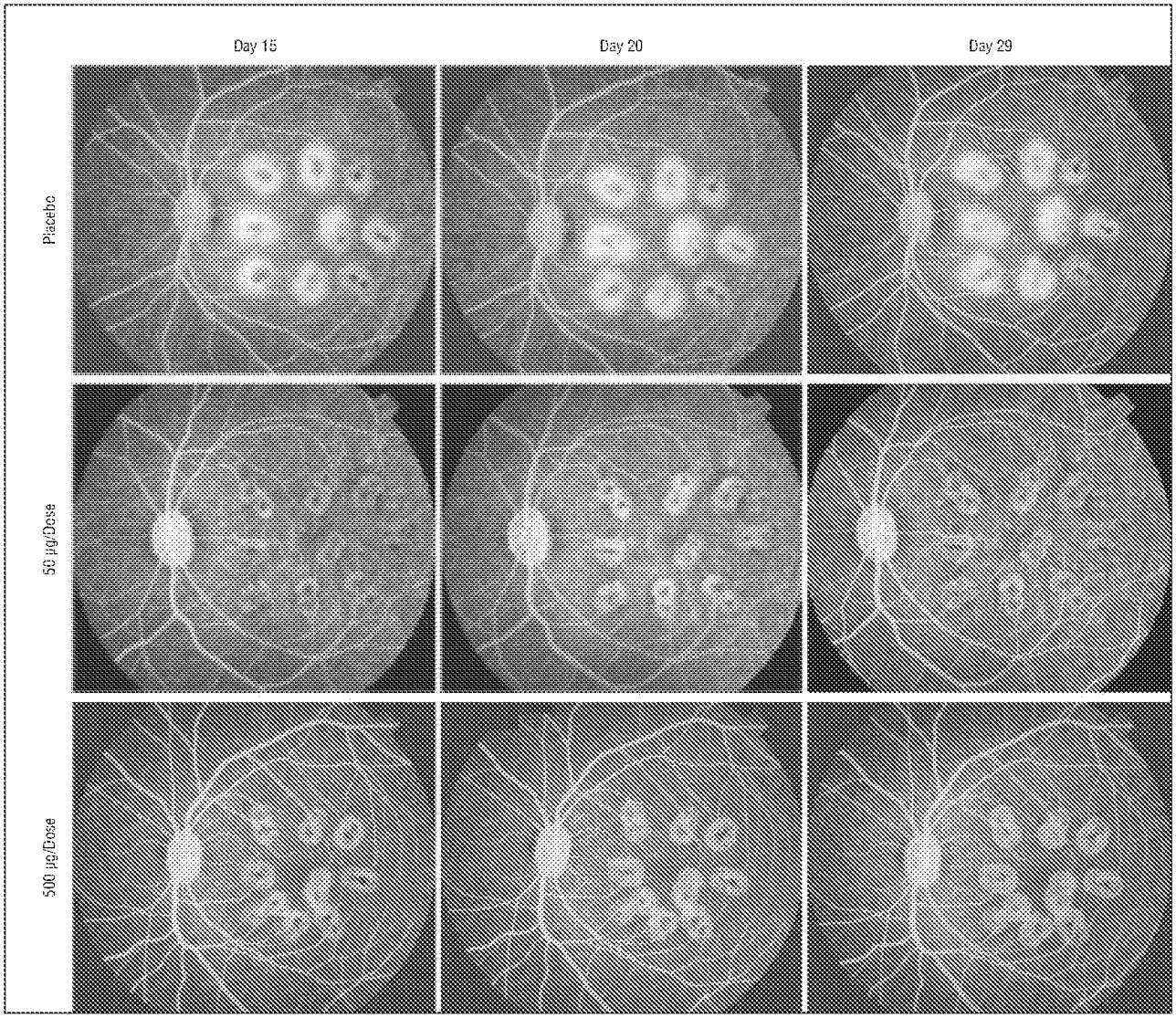

Figure 4. Intravitreous prevention (repeated injection) study, showing late-phase fluorescein angiograms at postlaser days 15, 20, and 29 for 3 representative animals in the indicated groups. The placebo-treated animal shows grade 4 leakage in most of the 9 treatment areas, whereas the animals in the groups receiving doses of 50 µg/eye and 500 µg/eye show no grade 4 leakage in any laser treatment areas at any of the 3 times.

to be approved for human use was pegaptanib (Macugen), an RNA aptamer directed against the VEGF-A 165 isoform.[15,16] Inhibition of VEGF-A 165 was shown to slow the progression of vision loss in wet AMD but did little to reverse vision loss. More recently, intravitreous administration of ranibizumab (Lucentis) has been approved for the treatment of AMD. Ranibizumab is a humanized monoclonal antibody Fab fragment that is directed against all isoforms of VEGF-A. It has largely replaced pegaptanib in clinical practice following 2 large, clinical, phase 3 trials (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA][17] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD [ANCHOR][18,19]) showing that 94% to 96% of patients receiving 0.5 mg of ranibizumab monthly lost fewer than 15 letters of visual acuity and 34% to 40% actually gained 15 letters. The related drug bevacizumab (Avastin), a humanized whole IgG1 antibody approved for oncology, is also used off label by clinicians.[20] Despite these advances, the current treatment of choice for AMD (either ranibizumab or bevacizumab) requires repeated intravitreous injections on a monthly basis for an indeterminate period—possibly years—to maintain improvements in visual acuity.

VEGF, PlGF, AND CNV

Extensive literature demonstrates that VEGF-A is a critical factor contributing to the development of ocular neovascularization (for a review, see the article by Witmer et al[21]). In contrast to other agents that bind and neutralize only VEGF-A, VEGF Trap also binds and neutralizes PlGF.[9] Placental growth factor is a member of the VEGF family of cytokines that is expressed prominently in the placenta, the tissue from which it was first isolated.[22] It can promote angiogenesis directly or by enhancing VEGF-A activity.[23-25] In contrast to VEGF-A, which also plays an indispensible role in normal vascular development, PlGF has been specifically implicated

in promoting pathological neovascularization. While genetic deletion of even a single allele of VEGF-A results in profound impairments in vascular development, normal vascular development and function are not appreciably impaired in PlGF-null mice. However, genetic deletion or pharmacological inhibition of PlGF significantly reduces pathological neovascularization as well as the associated vascular leakage in numerous disease settings.[26] Like VEGF-A, PlGF appears to be involved in promoting ocular vascular disease in both humans and animals. For example, PlGF is present in CNV membranes excised from human eyes,[27] and experimental CNV is decreased in PlGF-null mice and mice treated with PlGF neutralizing antibodies relative to controls.[28]

The proangiogenic and propermeability effects of VEGF-A are thought to be mediated primarily through VEGFR2 expressed on vascular endothelial cells. A structurally related receptor, VEGFR1, binds both VEGF-A and PlGF. In addition to being present on endothelial cells, where receptor ligation is also thought to promote angiogenesis and vascular permeability, albeit more weakly, VEGFR1 is expressed by many other cell types including leukocytes, pericytes, smooth muscle cells, and endothelial progenitor cells.[29] Thus, in addition to promoting angiogenesis and vascular permeability by acting directly on endothelial cells, VEGF and PlGF can also act via VEGFR1 on a variety of other cell types involved in blood vessel formation and stabilization. Moreover, VEGF and PlGF serve as potent chemoattractants and activators of leukocytes, particularly monocytes, in a variety of pathological conditions.[29,30]

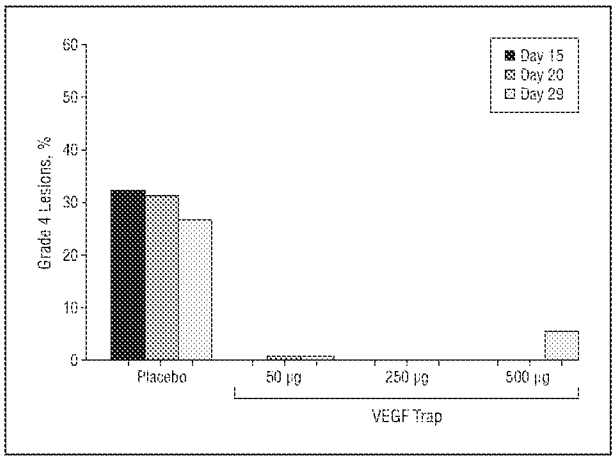

Figure 5. Percentage of grade 4 lesions at postlaser days 15, 20, and 29 for groups that received intravitreous placebo and VEGF Trap prevention.

EFFECTS OF VEGF TRAP IN RODENT MODELS OF OCULAR NEOVASCULARIZATION

VEGF Trap, administered either as serial subcutaneous injections or as a single intravitreous injection, has been shown to suppress laser-induced CNV in mice.[31] Moreover, VEGF Trap given subcutaneously inhibits retinal neovascularization in transgenic mice that overexpress VEGF in photoreceptors. Furthermore, VEGF Trap was found to reduce breakdown of the blood-retinal barrier following intravitreous injection of VEGF and in transgenic mice that overproduce VEGF in the retina.[31] Systemic administration of VEGF Trap also has been shown to suppress neovascularization and the associated inflammatory cell infiltrate following corneal injury[32] and to delay corneal allograft rejection in mice.[33] More recently, VEGF Trap has been reported to prevent the development and promote the regression of recently formed CNV following subretinal injection of matrigel in rats.[34] Interestingly, VEGF Trap treatment also reduced CNV-associated fibrosis and inflammation in this model.

THIS STUDY

Although CNV can be induced in other species,[35-37] only nonhuman primates have maculae similar to the human macula. Thus, the model by Ryan[11] of inducing CNV using intense, small laser spots applied to the macular retina to break the Bruch membrane has become a standard means of assessing the preclinical efficacy of pharmacological treatments for wet AMD (ie, CNV). For example, this model was used for preclinical evaluations of photodynamic therapy[38-41] and Lucentis.[10] Even so, the model has its limitations. The young nonhuman primates have otherwise healthy retinae (including retinal pigment epithelia) and the induced CNV, unlike CNV in elderly humans with AMD, is self-limiting, resolving in 6 to 8 weeks without treatment. Also, the model has considerable variability. Only about 40% of the treatment spots go on to develop grade 4 lesions[11] and 20% of the animals are nonresponders, with no CNV developing in either eye (T.M.N. and B.J.C., unpublished data, May 2008). Therefore, it is important to have an adequate number of subjects in each group.

Table 4. Percentages of All Grades of Choroidal Neovascular Lesions in the Prevention Groups at Postlaser Day 29

Group	Lesion Grade, %			
	1	2	3	4
Intravenous prevention				
Placebo	27.8	23.1	3.7	45.4
3 mg/kg/dose	87.0	11.1	0.9	0.9
10 mg/kg/dose	73.2	25.9	0.9	0.0
Intravitreous prevention				
Placebo	56.5	10.2	6.5	26.9
50 µg/eye/dose	83.3	15.7	0.0	0.9
250 µg/eye/dose	75.9	22.2	1.9	0.0
500 µg/eye/dose	79.6	13.0	1.9	5.6

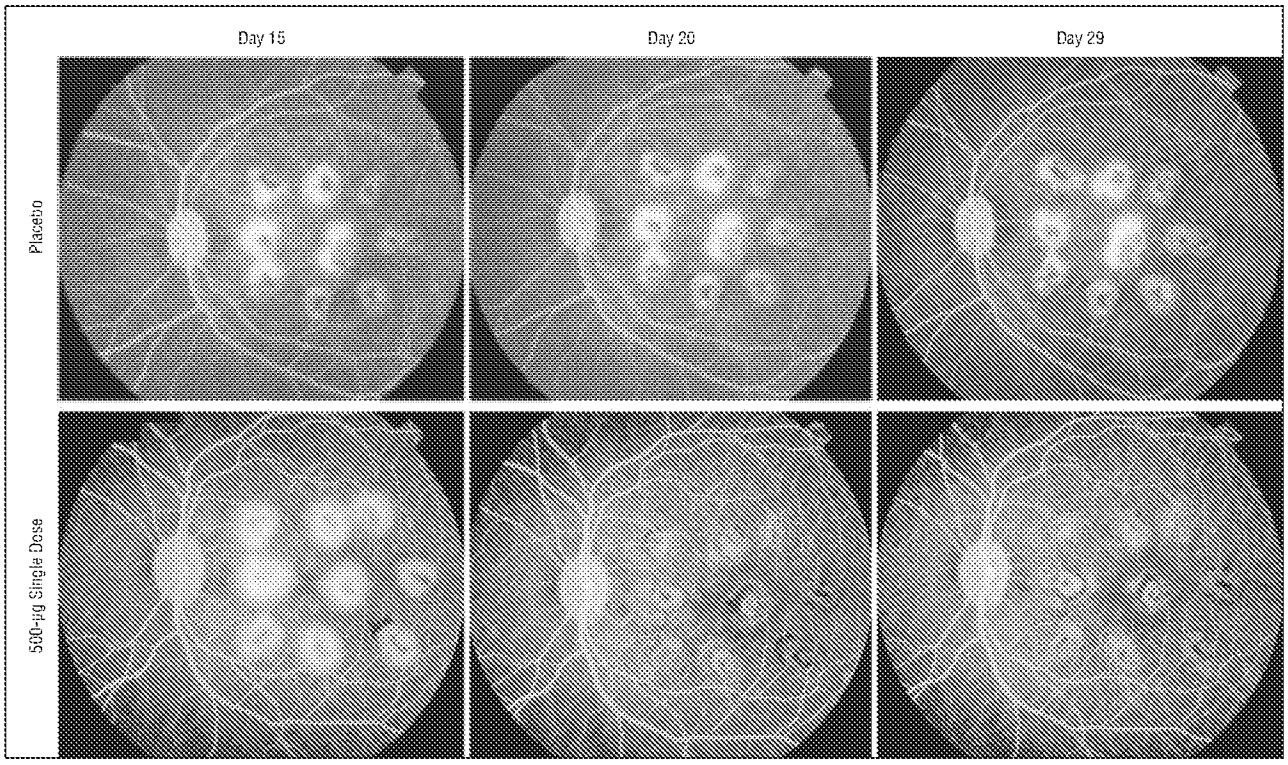

Figure 6. Intravitreous treatment study, showing late-phase fluorescein angiograms at postlaser days 15, 20, and 29 for representative animals in the groups receiving placebo and VEGF Trap treatment. The placebo-treated animal shows grade 4 leakage in most of the 9 treatment areas at all 3 times. The VEGF Trap–treated animal shows grade 4 leakage at all 9 laser sites on postlaser day 15 prior to receiving a single intravitreous injection of VEGF Trap. By postlaser day 20 (5 days following VEGF Trap injection), there are no grade 4 spots. No recurrence of grade 4 leakage is evident at postlaser day 29.

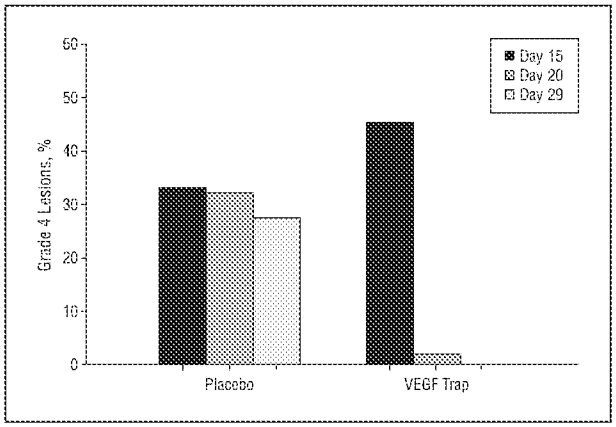

Figure 7. Percentage of grade 4 lesions at postlaser days 15, 20, and 29 for groups that received intravitreous placebo and a single treatment with 500 µg of VEGF Trap given on postlaser day 15.

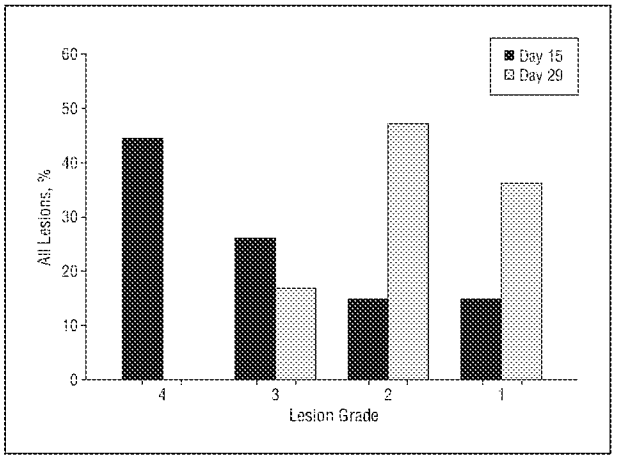

Figure 8. Percentage of all lesion grades at postlaser days 15 and 29 for a single intravitreous treatment with 500 µg of VEGF Trap given on postlaser day 15.

In this animal model of CNV, VEGF Trap was highly effective at preventing the development of grade 4 leakage on FA regardless of dose or whether it was administered intravenously on a weekly schedule or intravitreously every 2 weeks (Table 3, Figure 4, and Figure 5). Histological assessment confirmed that choroidal new vessel formation, fibrotic changes, and retinal thickness also were markedly less in the treated eyes (Table 5).

Moreover, when a single intravitreous injection of VEGF Trap was given after grade 4 CNV had developed, leakage was stopped within 5 days in approximately 95% of previously active grade 4 lesions and within 14 days following treatment in 100% of the lesions (postlaser days 20 and 29, respectively) (Table 3, Figure 6, and Figure 7). Although the effect of a single intravitreous injection of placebo was not evaluated, grade 4 lesions persisted for the duration of the study in all animals receiving multiple intravitreous or intravenous injections of placebo (Table 3). Histological examination revealed a trend toward decreased CNV and fibrosis relative to controls, which was not statistically significant. VEGF is a powerful mediator of vascular permeability in addition to new vessel formation, so VEGF Trap may have blocked VEGF-induced leakage from choroidal neovessels. Alterna-

Table 5. Histological Scores

Histological Finding	Score, Mean			
	CNV Prevention[a]		CNV Treatment[b]	
	Placebo	VEGF Trap	Placebo	VEGF Trap
Fibroplasia	1.74	1.05[c]	1.88	1.91
Retinal elevation	1.31	0.62[c]	1.62	1.43
Neovascularization	0.69	0.12[c]	0.90	0.58
Total	**3.74**	**1.79[c]**	**4.40**	**3.92**

Abbreviation: CNV, choroidal neovascularization.
[a]Mean scores for all lesions in all eyes (n = 6 per group).
[b]Mean scores for lesions that were grade 4 at postlaser day 15 (prior to the single VEGF Trap injection).
[c]$P < .05$, Mann-Whitney U test.

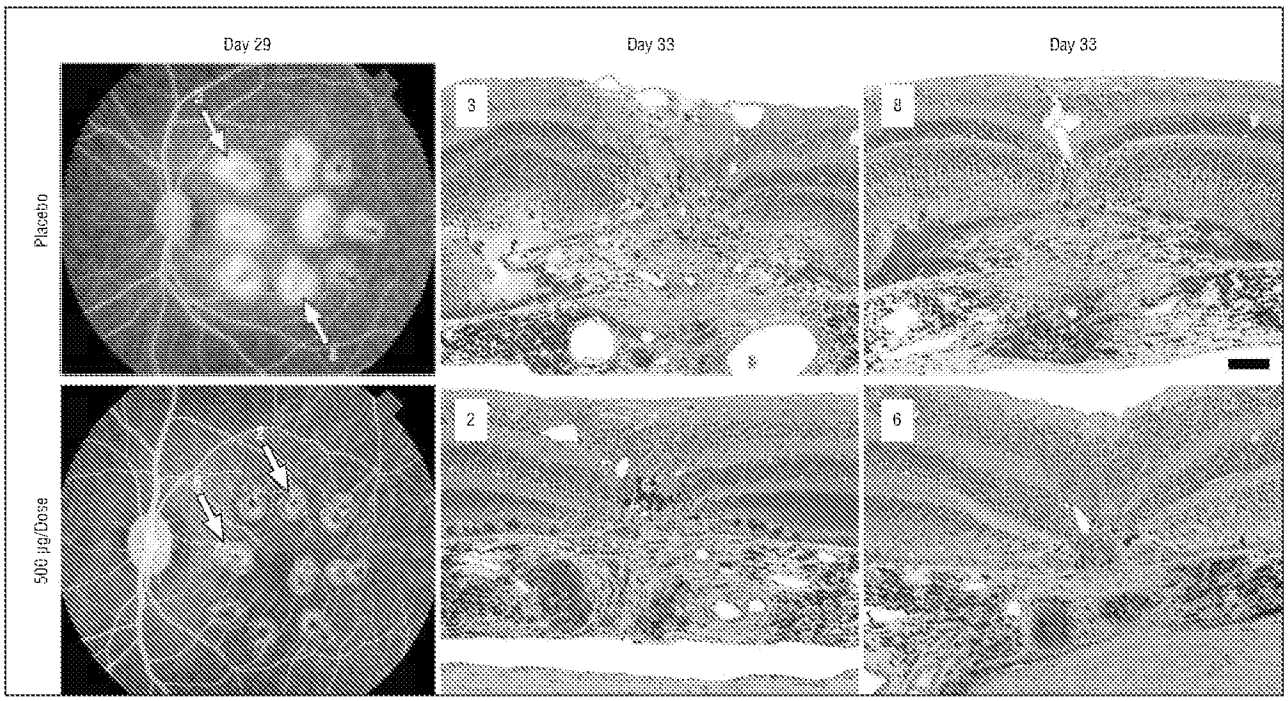

Figure 9. Intravitreous prevention study, showing late-phase fluorescein angiograms at postlaser day 29 and histological sections at postlaser day 33 (glycol methacrylate sections stained with toluidine blue; scale bar=250 µm) for 2 animals that received 3 intravitreous doses of either placebo or VEGF Trap (500 µg/eye/dose). The representative histological sections correspond to the numbered laser treatment areas in the fluorescein angiograms. The placebo-treated sections are thicker and more vascular compared with the VEGF Trap–treated eyes. Note the presence of subretinal fluid in lesion 3 on day 33.

tively, VEGF Trap may have reduced or stopped blood flow through the new vessels.

Intravitreous administration of VEGF Trap was well tolerated, with only a mild inflammatory response noted in the eyes that underwent intravitreous VEGF Trap treatment. Except for 1+ or fewer anterior chamber and vitreous cells in some eyes, no other ophthalmoscopic signs of inflammation were seen.

HUMAN TRIALS OF VEGF TRAP-EYE

VEGF Trap is now in clinical trials (for a recent review, see the article by Dixon et al[42]). A phase 1 trial of 25 patients with exudative AMD evaluated the tolerability and efficacy of intravenous administration of VEGF Trap at 3 different dose levels. Subjects had a significant decrease in retinal thickness as determined by optical coherence tomography,[43] although visual acuity was not significantly improved in this small safety study. However, 1 subject experienced grade 4 hypertension and 1 subject developed grade 2 proteinuria. Hypertension and proteinuria are now well-established class effects of systemic VEGF inhibition, and both patients exhibiting these adverse events in the study by Nguyen et al[43] had received the highest intravenous dose of VEGF Trap (3 mg/kg).

Another phase 1 study (Clinical Evaluation of Anti-angiogenesis in the Retina, CLEAR-IT 1) used intravitreous administration of VEGF Trap-Eye (aflibercept ophthalmic solution).[44] The first part of this study was a sequential cohort dose escalation (from 0.05 to 4.0 mg/eye) in 21 patients with exudative AMD. No serious systemic or ocular toxic effects were observed. However, a marked decrease in retinal thickness[44] and improvement in visual acuity[44] were noted. VEGF Trap-Eye also

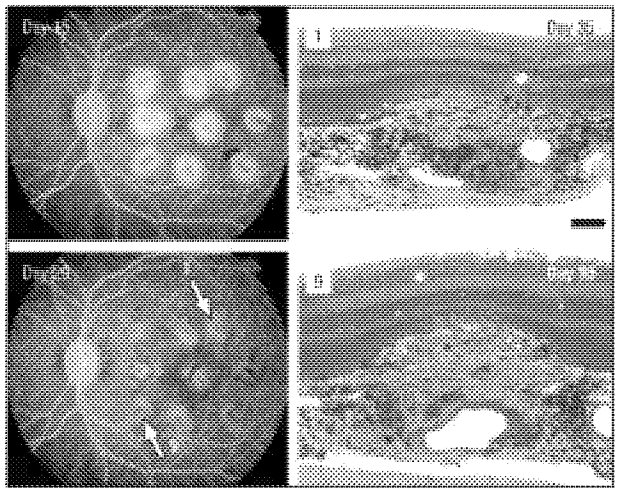

Figure 10. Intravitreous treatment study, showing late-phase fluorescein angiograms at postlaser days 15 and 29 and histological sections (corresponding to the numbered laser treatment areas in the day 29 fluorescein angiogram) obtained at necropsy on postlaser day 35 (glycol methacrylate sections stained with toluidine blue; scale bar=250 μm) from an animal that was treated with a single intravitreous 500-μg dose of VEGF Trap on day 15 following angiography. Note the marked reduction in fluorescein leakage from all of the treatment areas on the day 29 angiogram. In the histological sections, lesions are somewhat thicker and contain more patent choroidal new vessels than was observed in the VEGF Trap prevention study (Table 5 and Figure 9).

has been used in a small open-label safety study for treatment of diabetic macular edema.[45] A single dose of 4 mg was administered intravitreously to 5 patients who had undergone multiple prior treatments for diabetic macular edema. There was a median decrease in central macular thickness of 79 μm as well as some improvement in vision. A phase 2 trial in diabetic macular edema is in progress.

In a double-masked phase 2 trial (CLEAR-IT 2), VEGF Trap-Eye was evaluated in 157 patients with exudative AMD randomized to either monthly or quarterly intravitreous injections for 12 weeks at doses of 0.5 or 2 mg (monthly injections) and 0.5, 2, or 4 mg (quarterly). Following the 12-week fixed dosing period, patients continued to receive treatments on an as-needed basis at their originally assigned dosages. Reports of the 1-year results described a statistically significant improvement in vision, retinal thickness, and size of the CNV lesions,[46,47] with few re-treatments required during the 40-week phase of as-needed treatment. Patients initially dosed on a schedule of 2.0 mg monthly received, on average, only 1.6 additional injections during the 40-week period of as-needed treatment, and those initially dosed on a schedule of 0.5 mg monthly received, on average, 2.5 injections. While as-needed dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity at week 52 as compared with baseline, the results generally were not as robust as those obtained with initial fixed monthly dosing. VEGF Trap-Eye was generally well tolerated and there were no drug-related serious adverse events. The most common adverse events were those typically associated with intravitreous injections.

Two phase 3 trials of 2 years' duration are under way to further investigate the efficacy and safety of VEGF Trap-Eye in wet AMD, VIEW 1 in the United States and Canada[48] and VIEW 2 in Europe, Japan, and Latin America.[49] For both trials, VEGF Trap-Eye is being administered intravitreously. In the first year of treatment, VEGF Trap-Eye was administered every 4 weeks at doses of either 0.5 or 2 mg. Another study arm used 3 initial monthly doses of 2 mg followed by 2-mg doses given at 8-week intervals. The active control arm comprised subjects receiving ranibizumab (0.5 mg) at 4-week intervals. The 1-year outcomes from these studies are pending publication.

CONCLUSIONS

Using an established primate model of CNV, administration of VEGF Trap in a prevention protocol markedly reduced vasoproliferative responses of the macaque retina to laser injury, substantially preventing the development of all components of CNV lesions as well as vascular leakage. When a single intravitreous VEGF Trap injection was given after grade 4 lesions had developed, there was resolution of vascular leakage. This also resulted in a trend toward lower histological scores for the neovascular components of the lesions, suggesting partial regression of newly formed vessels.

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Additional Contributions: Huihao Fan, MA, and Ajit Thakur, PhD, provided the statistical analysis.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Patent No. 10,828,345
Issue Date: November 10, 2020
Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Case: PGR2021-00035

PETITION FOR POST-GRANT REVIEW

UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200 et seq.

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Dixon *et al.*, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," (2009) 18(10):1573-1580	1048

I. INTRODUCTION

Petitioner Chengdu Kanghong Biotechnology Co., Ltd. ("Petitioner" or "Kanghong") respectfully petitions for post grant review ("PGR") in accordance with 35 U.S.C. §§ 321-329 and 37 C.F.R. § 42.200 *et seq*. of all claims of U.S. Patent No. 10,828,345 (the "'345 patent" (Ex. 1001)), which issued on November 10, 2020 to Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron"). As shown in this petition, all claims are invalid as anticipated, obvious, and lacking written description support.

The '345 patent is premised on the supposed "surprising discovery" that VEGF antagonists are effective with "less frequent dosing . . . compared to prior administration regimens for angiogenic eye disorders which require monthly administrations." Regeneron was not the first to have this revelation. In a PCT application ("Shams")[1] filed more than six years and published almost five years earlier, Genentech described the same discovery: "It has been discovered that the treatment effects of a VEGF antagonist, e.g., Ranibizumab, are maintained for an extended period of time, such as more than one month." [2]

[1] Ex. 1004.

[2] Ex. 1004, Page 24, Lines 27-28.

The '345 patent describes methods of treating angiogenic eye disorders with an initial dose, one or more secondary doses, and one or more tertiary doses of a specific VEGF antagonist. Shams describes the same regimen and the VEGF antagonist. The '345 patent's only independent claim limits this dosing regimen by specifying that each secondary dose is administered every 4 weeks and each tertiary dose is administered every 12 weeks. That dosing frequency is also described in Shams. The '345 patent is thus anticipated by Shams.

The '345 patent is also obvious over Regeneron's own prior art press release publicizing the claimed dosing regimens. During prosecution, Regeneron overcame its own press release (the "2009 Press Release") [3] by focusing on the 12–week tertiary dosing frequency as the supposedly inventive aspect of the claims. But the 12–week tertiary dosing frequency was known, as evidenced by Shams. Although the 2009 Press Release expressly disclosed a 12–week tertiary dose, Regeneron argued that "[m]ere mention of a prospective possibility of dosing at 12 weeks does not specifically indicate or teach towards a method where 12–week dosing would be undertaken, let alone successful."[4] To the extent the 2009 Press release did not adequately disclose a 12–week tertiary dose, the 2009 Press Release

[3] Ex. 1005.

[4] Ex. 1002, Response to Office Action 03/16/2020, Page 4.

in combination with Shams renders the claims obvious. One of skill in the art would have been motivated to combine the Shams 12–week tertiary dosing regimen with the 2009 Press Release because Shams, in listing suitable VEGF antagonists for the regimen, specifically identifies Regeneron's VEGF Trap.[5] Thus, the '345 patent is invalid as obvious over the 2009 Press Release in view of Shams.

Regeneron's prosecution arguments about the 2009 Press Release also support a finding that the '345 patent is invalid as lacking written description. Regeneron argued during prosecution that one of skill in the art "would not have understood a . . . dosing regimen with 4 and 12 week limits as encompassing a q12w regiment," but the '345 patent specification provides the same disclosure. Regeneron also argued during prosecution that the disclosure of a 12–week dosing "possibility" was insufficient to identify a 12–week dosing, but the '345 patent specification does not differentiate a 12–week tertiary dosing regimen from myriad other possibilities; such "undifferentiated descriptions" of a specific invention are insufficient to satisfy 35 U.S.C. § 112(a). *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346 (Fed. Cir. 2013).

[5] Wu Decl. (Ex. 1003) at ¶ 112.

The '345 patent is eligible for PGR. The '345 patent is a "transition" application, filed after the America Invents Act ("AIA") went into effect but claiming priority to several pre-AIA applications. Under the AIA, a patent that issues from a transition application is eligible for PGR if it contains a claim that lacks written description support in a pre-AIA application. Claim 8 of the '345 patent recites "branch retinal vein occlusion," a disorder that was first mentioned in a continuation-in-part (CIP) patent application filed on July 12, 2013. Thus, the '345 patent is eligible for PGR. Further, because the '345 specification does not provide written description support for the claimed 12–week tertiary dosing frequency, none of the pre-AIA priority applications provides written description support for the '345 patent claims. As a result, the '345 patent's earliest effective filing date is its actual filing date, October 12, 2018, making the patent eligible for PGR for this separate reason.

The Board should institute PGR and find all of the claims unpatentable under 35 U.S.C. §§ 102, 103, and 112.

II. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.204(a), Kanghong certifies that the '345 patent is available for PGR and that Kanghong is not barred or estopped from requesting PGR on the grounds identified in this Petition. Specifically: (1) neither Kanghong nor any of its privies own the '345 patent; and (2) neither Kanghong nor any of its

privies have filed a U.S. civil action challenging the validity of any claim of the '345 patent.

Despite claiming priority to applications filed before the effective date of the AIA, the '345 patent is eligible for PGR pursuant to Section 3(n)(1) of the AIA[6] because multiple granted claims do not find Section 112 support in any of the pre–AIA applications. As explained below, the '345 patent has an earliest effective filing date in July 2013 or October 2018, thus rendering it eligible for PGR.

III. STATEMENT OF RELIEF REQUESTED

Kanghong requests review under 35 U.S.C. § 321 of claims 1-11 of the '345 patent, and seeks a finding that claims 1-11 are unpatentable as anticipated under 35 U.S.C. § 102(a), as obvious under 35 U.S.C. § 103, and for lacking written description support under 35 U.S.C. § 112(a).

IV. THE '345 PATENT

On October 12, 2018, Regeneron filed U.S. Application No. 16/159,282 (the "'282 application"), which matured into the '345 patent.[7] The '345 patent, titled

[6] Pub. L. No. 112-29, AIA § 3(n)(1), *LEAHY–SMITH AMERICA INVENTS ACT*, PL 112-29, 125 Stat. 284, 293 (Sept. 16, 2011).

[7] Ex. 1001, Cover Page.

"Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders,"[8] has one independent claim:[9]

> A method for treating an angiogenic eye disorder in a patient, said method comprising
>
> sequentially administering to the patient
>
> [a] a single initial dose of a VEGF antagonist,
>
> [b] followed by one or more secondary doses of the VEGF antagonist,
>
> [c] followed by one or more tertiary doses of the VEGF antagonist;
>
> [d] wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and
>
> [e] wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;
>
> [f] wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-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.

[8] *Id.*

[9] *Id.* at Col. 21:56-23:14.

Claim 1 has three sequential steps:[10] (1) administer an initial dose of a specific VEGF antagonist (step [a], narrowed by clause [f]): (2) administer one or more secondary doses, each 4 weeks after the immediately preceding dose (step [b], narrowed by clause [d]); and (3) administer one or more tertiary doses, each 12 weeks after the immediately preceding dose (step [c], narrowed by clause [e]).

The '345 patent includes ten dependent claims. These claims narrow independent claim 1 by specifying the drug administered (claim 2),[11] modes of administration (claims 3 and 4),[12] dose amount (claims 5-7),[13] and the disorder(s) treated (claims 8-11).[14]

A. Background: VEGF Trap and AMD

Vascular endothelial growth factor (VEGF) is a promoter of angiogenesis and causes ocular disorders such as neovascular age-related macular degeneration

[10] Ex. 1003 at ¶ 67.

[11] *Id.* at ¶ 68 (citing Ex. 1001, Col. 22:56-57).

[12] Ex. 1003 at ¶ 68 (citing Ex. 1001, Col. 22:58-62).

[13] Ex. 1003 at ¶ 68 (citing Ex. 1001, Col. 22:63-23:2).

[14] Ex. 1003 at ¶ 68 (citing Ex. 1001, Col. 23:3-13).

("AMD"[15]).[16] For many decades, VEGF antagonists have been known to inhibit VEGF and have proven to be an effective strategy in treating diseases involving pathological angiogenesis, such as AMD.[17]

Many VEGF antagonists have received FDA approval for AMD. For example, Ranibizumab, an anti-VEGF antibody manufactured by Genentech, received FDA approval for treatment of AMD in 2006.[18] Regeneron developed Aflibercept and received FDA approval for treatment of AMD in November 2011.[19]

B. '345 Patent's Specification

The '345 patent's "Background" acknowledges that the prior art includes "FDA-approved treatments of angiogenic eye disorders [which] include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®,

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[15] Neovascular AMD is also referred to as "Wet AMD." In this petition, "AMD" is used to refer to neovascular/wet AMD.

[16] Ex. 1003 at ¶ 50.

[17] *Id.* at ¶¶ 56-60.

[18] Ex. 1006; *see also* Ex. 1001, Col. 2:30-31 (citing "prescribing information for Lucentis® [ranibizumab], Genentech, Inc.").

[19] Ex. 1001, Col. 2:51-52; *see also* Ex. 1007.

Genentech, Inc.) on a monthly basis by intravitreal injection" but identifies a "need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy."[20] The "Summary of Invention" describes the inventor's contribution to the art as "less frequent dosing" than, e.g., Genentech's ranibizumab:[21]

> The present inventors [sic] have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. . . . One advantage of such a dosing regimen is that, for most of the course of treatment (i.e., the tertiary doses), it allows for less frequent dosing (e.g., once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (See, e.g., prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

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[20] Ex. 1001, Col. 1:57-67.

[21] *Id.* at Col. 2:12-31 (modification "[ranibizumab]" in original).

The Detailed Description begins with a section titled "Dosing Regimens," which explains the meanings of "initial dose," "secondary dose," and "tertiary dose:"[22]

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

The '345 patent has little discussion of 12–week tertiary dosing. When a 12–week tertiary dose is mentioned, the '345 patent includes it as one of 14 "or more" possible tertiary dosing frequencies: "each tertiary dose is administered at least 8 (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, **12**, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose."[23] When the '345 patent next mentions a 12–week dose frequency, the 12–week dose(s) is preceded by four 8–week "tertiary doses" and 12 weeks is again only one choice, among many, for the

[22] *Id.* at Col. 3:42-56.

[23] *Id.* at Col. 3:60-62 (emphasis added).

subsequent tertiary dose.[24] Because the tertiary dosing in this description includes 8–week dosing followed by 12–week dosing, it does not describe the claimed 4–week secondary dosing followed by "each tertiary dose is administered 12 weeks after the immediately preceding dose."[25] The remainder of the '345 patent includes no discussion of a dosing regimen where "each tertiary dose is administered 12 weeks after the immediately preceding dose." The only other mention of 12 weeks is as an upper limit of a PRN[26] regimen,[27] the same dosing regimen recited in Patent Owner's 2009 Press Release and distinguished by Patent Owner during prosecution.

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[24] *Id.* at Col. 4:41-43 ("each subsequent tertiary dose is administered from 8 to 12 (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, **12**) weeks after the immediately preceding dose") (emphasis added).

[25] This discussion in the '345 patent corresponds to Claim 5 of the parent PCT Application. That claim does not teach "sequentially administering" secondary doses and tertiary doses of the same frequency for the same reasons as the corresponding paragraph in the '345 patent.

[26] "PRN" is an abbreviation for "*pro re nata*" meaning "as needed." Ex. 1003 at ¶ 62.

[27] Ex. 1001, Col. 10:4-25.

C. Regeneron's Clinical Trials and 2009 Press Release of VEGF Treatments for Angiogenic Eye Disorders

In 2005, Regeneron began a Phase 1 study for VEGF Trap treatment of AMD with a single dose per patient.[28] Regeneron announced preliminary positive results in the Phase 1 study on May 1, 2006.[29] The Phase 1 study is described in Example 1 of the '345 patent.[30]

In May 2007, Regeneron presented interim results of a Phase 2 VEGF Trap trial in AMD, describing dosing regimens comprising a single initial dose and one or more secondary doses at 4 or 12–week intervals for the first 12 weeks of treatment.[31] The arms of the Phase 2 study are described in Example 2 of the '345 patent.[32]

On September 14, 2009, Regeneron, through the 2009 Press Release, announced a Phase 3 trial with various initial, secondary, and tertiary doses.[33] This

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[28] Ex. 1008.

[29] Ex. 1009.

[30] Ex. 1003 at ¶ 74.

[31] Ex. 1010.

[32] Ex. 1003 at ¶ 75.

[33] Ex. 1005.

trial is disclosed as Example 4 of the '345 patent.[34] According to the 2009 Press Release, after the first year of initial and 4–week secondary dosing, patients would continue to be followed and treated for another year on a flexible, criteria-based extended PRN regimen with a dose administered between four and 12 weeks.[35]

D. '345 Patent's Prosecution History

The '345 patent claims priority to a provisional application (the first of three) filed in January 2011, more than one year after the 2009 Press Release, through a PCT application filed January 2012, a CIP application filed July 2013, and a series of continuations of the CIP.[36] The PCT application and three provisional applications are the only pre-AIA applications in the family.[37]

The '282 application originally presented two independent claims, claim 21 (abandoned in prosecution) and claim 32 (issued as claim 1 of the '345 patent). In a first action, the PTO rejected all claims for obviousness type double patenting

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[34] Ex. 1003 at ¶ 77.

[35] *Id.*

[36] *Id.*

[37] Ex. 1001, Cover Page. The PCT, the CIP, and the continuation applications all claim priority to the three provisional applications.

over seven Regeneron patents.[38] After the first action (but before Regeneron's response), a "Third Party Submission" disclosed the 2009 Press Release to the PTO.[39]

Regeneron overcame the double patenting rejection by repeating the purported inventiveness of non-monthly dosing. In characterizing the state of the art, Regeneron told the PTO that the "standard of care for the treatment of [AMD] was to administer an antibody formulation (ranibizumab) by injection to the eye once per month."[40] Turning to the claimed invention, Regeneron said that "by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent [claim 1], it is possible to treat angiogenic eye disorders . . . on a less frequent basis than previously thought possible."[41]

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[38] Ex. 1002, Rejection, 04/03/2019.

[39] Ex. 1002, Office Communication, 05/31/2019. Neither Petitioner nor its affiliates filed the Third-Party Submission. The record does not reflect who filed the Third-Party Submission, and Petitioner is unaware of the identity of the filer.

[40] *Id.*

[41] *Id.*

In the next action, the PTO withdrew the double patenting rejection and added a rejection of (now) claims 1-11 as anticipated by the 2009 Press Release.[42] To overcome the 2009 Press Release, Regeneron argued that claims 1-11 "require[e] tertiary dosing administered 12 weeks after the immediately preceding dose" and discussed no other limitations of the claims.[43] In distinguishing the disclosure of the 2009 Press Release, Patent Owner argued that "[m]ere mention of a prospective possibility of dosing at 12 weeks does not specifically indicate or teach towards a method where 12–week dosing would be undertaken, let alone successful."[44] The Examiner explicitly relied on this argument to allow claims 32-42,[45] which issued on November 10, 2020 as claims 1–11 of the '345 patent.[46]

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[42] Ex. 1002, Rejection, 10/01/2019, Pages 4-5.

[43] Ex. 1002, Response, 03/16/2020, Page 4.

[44] *Id.* at 5; *see also* (Ex. 1002, Response, 01/23/2020, Pages 6-7 (The 2009 Press Release "does not disclose tertiary dosing administered 12 weeks after the immediately preceding dose. Accordingly, the press release does not anticipate the claims and the rejection should be withdrawn.")).

[45] Ex. 1002, Notice of Allowance, 04/01/20, Pages 2-3.

[46] Ex. 1001, Cover Page.

E. Level of Ordinary Skill in the Art

At the time of invention, a person of ordinary skill in the art of the '345 patent would have been a person with a medical doctorate, an internship and residency in ophthalmology, and a 1-year medical retina fellowship or 2-year vitreoretinal surgical fellowship.[47] A person with less education but more relevant practical experience with retinal disease treatment may also be a person of ordinary skill in the art.[48]

V. CLAIM CONSTRUCTION

Pursuant to 83 Fed. Reg. 51340, a claim is construed using the standard set forth by *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). Petitioner relies on the plain language of the claims in the '992 patent to demonstrate that the claims are anticipated and/or obvious in light of the prior art. Accordingly, a formal claim construction is unnecessary. *See Hakim v. Cannon Avent Grp., PLC*, 479 F.3d 1313, 1318-19 (Fed. Cir. 2007) ("When there is no dispute as to the meaning of a term that could affect the disputed issues of the litigation, 'construction' may not be necessary."); *Vivid Techs., Inc.*, 200 F.3d at

[47] Ex. 1003 at ¶ 82.

[48] *Id.*

803 (only those terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy).[49]

VI. THE '345 PATENT IS ELIGIBLE FOR PGR

A patent is eligible for PGR if it "contains or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after [March 16, 2013]." AIA §§ 3(n)(1), 6(f)(2)(A). The "effective filing date" of a patent is defined under 35 U.S.C. § 100(i)(1)(B) as "the filing date of the earliest application for which the patent . . . is entitled, as to such invention, to a right of priority under section 119, 365(a), or 365(b) or to the benefit of an earlier filing date under section 120, 121, or 365(c)." In order for a patent application to be entitled to a "right of priority" or "an earlier filing date" based upon an earlier filed application, the earlier filed application must have been disclosed "in the manner provided by section 112(a) (other than the requirement to disclose the best mode)." 35 U.S.C. § 119(e)(1); 35 U.S.C. § 120.

[49] Petitioner reserves the right to propose constructions for claim terms in this proceeding in response to arguments raised by Patent Owner in any future submission.

Accordingly, for purposes of determining PGR eligibility, a patent application may rely on the filing date of an earlier filed application only if it is described in the manner provided by 35 U.S.C. § 112(a), including written description support for the claims. If an application is not entitled to claim priority to a prior application, the effective filing date for the patent is the "actual filing date of the patent or the application for the patent containing a claim to the invention." 35 U.S.C. § 100(i)(1)(A). Here, that means that the '345 patent's earliest effective filing date is either in July 2013 or in October 2018. The '345 patent is thus eligible for PGR.

That the '345 patent is a continuation "transition" application does not affect the requirements for PGR eligibility.

A. "[T]he Angiogenic Eye Disorder Is . . . Branch Retinal Vein Occlusion" of Claim 8 Is not Supported by a Pre-AIA Application

Claim 8 includes the indication "branch retinal vein occlusion," which first appeared[50] in the '345 patent's family when Regeneron filed U.S. Application No. 13/940,370 (the "'370 application") on July 12, 2013, as a CIP of the PCT application.[51] The '345 patent, and its grandparent '370 application, thus contains at least one claim that has an effective filing date on or after March 16, 2013.

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[50] Ex. 1011, at ¶ 0026 and claim 6.

[51] Ex. 1001, Cover Page.

"[S]ome subject matter of a CIP application is *necessarily different* from the original subject matter." *Uni. of W. Va. Bd. of Trustees v. VanVoorhies*, 278 F.3d 1288 (Fed. Cir. 2002) (citing MPEP § 201.08 (7th ed. Rev. 1 Feb. 2000)) (emphasis added). The CIP's new subject matter is the additional eye disorders not disclosed in earlier filed patent applications, such as branch retinal vein occlusion ("BRVO").

In the CIP application, BRVO appears in a section titled "Angiogenic Eye Disorders," which consists of the paragraph below.[52] To illustrate the subject matter added to the CIP, the paragraph below compares the pre and post 2013 paragraph, where underlined text indicates subject matter not appearing in the '370 application's parent, *italics* indicates text moved in the paragraph, and *italics* with strikethrough indicates the original position of the moved text (no text was deleted[53]).

> The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that

[52] Ex. 1011; *see also* Ex. 1003 at ¶ 120.

[53] Ex. 1003 at ¶ 123.

> are treatable using the methods of the present invention include ~~*choroidal neovascularization*~~, age-related macular degeneration (e.g., wet AMD, ~~*diabetic retinopathies,*~~ exudative AMD, etc.), retinal vein occlusion (RVO), ~~*diabetic macular edema (DME),*~~ central retinal vein occlusion (CRVO; e.g., macular edema following CRVO), branch retinal vein occlusion (BRVO), *diabetic macular edema (DME), choroidal neovascularization* (CNV; e.g., myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, *retinal neovascularization*, vitreal neovascularization, pannus, pterygium, vascular retinopathy, and *diabetic retinopathies* ~~*retinal neovascularization*~~.

BRVO was neither explicitly nor implicitly disclosed in the pre-AIA applications.[54] As the above paragraph demonstrates, the PCT application (i.e., the latest pre-AIA application) was completely silent about BRVO, and it was only added in the AIA CIP application. Having examined the pre-AIA indications, one of skill in the art in 2011-13 would have recognized that all of the listed disorders are different from BRVO; for example, each has different pathologies and has

[54] *Id.* at ¶ 120-24.

different standards for treatment.[55] One of skill in the art would not understand that successful treatment of one vascular disease (e.g., choroidal neovascularization, AMD, diabetic retinopathies, DME, CRVO, corneal neovascularization, or retinal neovascularization) means another (e.g., BRVO) is necessarily treated.[56]

Other disclosures within the specification reinforce the inventor's failure to possess a treatment for BRVO. In the "Background," the PCT application identifies various eye disorders treatable by VEGF antagonists, but nowhere mentions BRVO.[57] Similarly, the "Treatment Population and Efficacy" section identifies various disorders treatable by the "present invention," but no mention of BRVO.[58] The examples describe various disorders studied in the clinical trials, but none of the examples in pre-AIA applications (i.e., Examples 1-6) mention BRVO.[59]

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[55] *Id.* at 124.

[56] *Id.* at 124-25.

[57] Ex. 1001, Col. 1:31-61 (the CIP did not modify this teaching).

[58] *Id.* at Col. 7:26-44.

[59] Example 7 was added with the CIP '370 application. The additional eye disorders are the only subject matter in Example 7 not supported by the PCT.

The pre-AIA applications' discussion of "central retinal vein occlusion" ("CRVO") does not constitute a written description of BRVO. One of skill in the art would not recognize a disclosed treatment of CRVO to be possession of a treatment for BRVO.[60] These are different indications, with their own standard of care in 2012–13.[61] Anatomically, they are different.[62] Further, they affect populations differently—Asians and Hispanics appeared to have an elevated risk of BRVO compared to Caucasians, whereas no similar difference was found for CRVO.[63] The specification and prosecution history confirm that CRVO and BRVO are different—Patent Owner claimed BRVO as a separate indication from CRVO and amended the specification to explicitly recite BRVO, confirming that one of skill in the art would recognize that BRVO and CRVO are separate indications.[64] Consistently, Regeneron conducted separate trials for BRVO and CRVO.[65]

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[60] Ex. 1003 at ¶¶ 126-29.

[61] *Id.* at ¶ 127.

[62] *Id.* at ¶ 126.

[63] *Id.*

[64] *Id.* at ¶ 130.

[65] *Id.* at ¶ 131.

Accordingly, none of the pre-AIA applications provides adequate written description support for claim 8[66] of the '345 patent. The patent is therefore eligible for PGR.

B. The Dosing Regimen of Claim 1 Is not Supported by a Pre-AIA Application

As explained in Section VIII below, the '345 patent is invalid under 35 U.S.C. § 112(a) for failing to support the claimed 12–week tertiary dosing regimen. That regimen first entered the patent family when Regeneron filed the '345 patent. For this reason, the earliest filing date of the '345 patent is its actual filing date, October 28, 2018, making the patent eligible for PGR.

VII. GROUNDS 1 & 2: THE '345 PATENT'S CLAIMS ARE ANTICIPATED AND OBVIOUS

Petitioner respectfully requests the Board cancel all claims of the '345 patent on the following prior-art grounds:

Ground 1: Claims 1-11 are anticipated by Shams under pre-AIA 35 U.S.C. § 102(b) and post-AIA 35 U.S.C. § 102(a)(1).

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[66] Additionally, the '345 patent is eligible for PGR because a post-AIA application in its priority chain, the '370 application, includes a claim ('370 application claim 6) which is not supported by a pre-AIA patent application. The '370 application claim 6 includes the same list of disorders as the '345 patent claim 8.

Ground 2: Claims 1-11 are rendered obvious by the 2009 Press Release in view of Shams under pre-AIA 35 U.S.C. § 103 and post-AIA 35 U.S.C. § 103.

A. Ground 1: The '345 Patent's Claims Are Anticipated by Shams

1. Shams

Shams published on May 4, 2006 and thus is prior art to the '345 patent under pre-AIA 35 U.S.C. § 102(b) and 35 U.S.C. §§ 102(a)(1) and (2). Shams discloses effective VEGF antagonist treatments with extended dosing frequencies: "It has been discovered that the treatment effects of a VEGF antagonist, e.g., Ranibizumab, are maintained for an extended period of time, such as more than one month."[67] Exemplary VEGF antagonists provided in Shams include Regeneron's VEGF trap.[68] Six years after Shams' filing and five years after its publication, the '354 patent described the same "surprising discovery:"[69]

> The present inventors [sic] have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by

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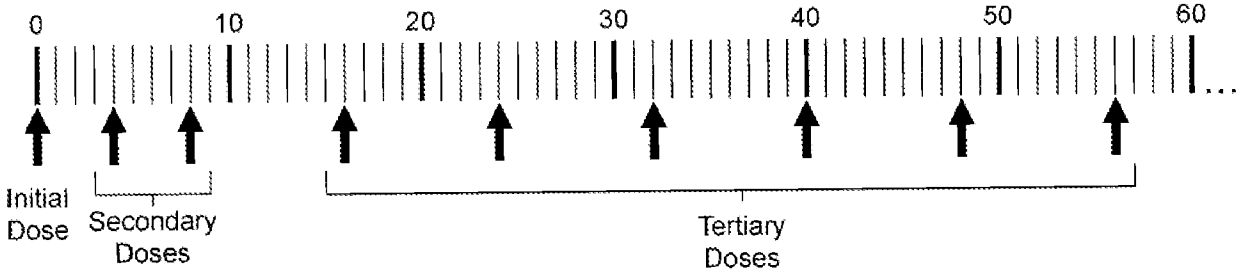
[67] Ex. 1004, Page 21, Lines 27-28.

[68] *Id.* at Page 6, Lines 27-33.

[69] Ex. 1001, Col. 2, Lines 12-31 (emphasis added) (modification "[ranibizumab]" in original).

> about three doses administered to the patient at a frequency of about 2 to 4 weeks. . . . One advantage of such a dosing regimen is that, for most of the course of treatment (i.e., the tertiary doses), *it allows for less frequent dosing (e.g., once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations* throughout the entire course of treatment. (See, e.g., prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

Like the '345 patent, Shams describes a dosing regimen of "initial, secondary, and tertiary" doses. Shams uses different terms ("first individual doses" and "second individual doses") to describe the dosing scheme, but the difference is in name only.[70] The '345 patent Figure 1 illustrates the "initial dose," "secondary doses," and "tertiary doses:"



[70] Ex. 1003 at ¶¶ 90, 96.

Shams Figure 2 "illustrates a dosing regimen for treating, e.g., age-related macular degeneration (AMD) with a VEGF antagonist."[71] The figure includes three groups: Group 1 received a 0.3 mg dose of VEGF antagonist; Group 2 received a 0.5 mg dose of VEGF antagonist; and Group 3 received a sham injection.[72] Each group illustrates an initial dose at "month 0," two secondary doses at "month 1" and "month 2," and subsequent tertiary doses every 3 months thereafter until two years.

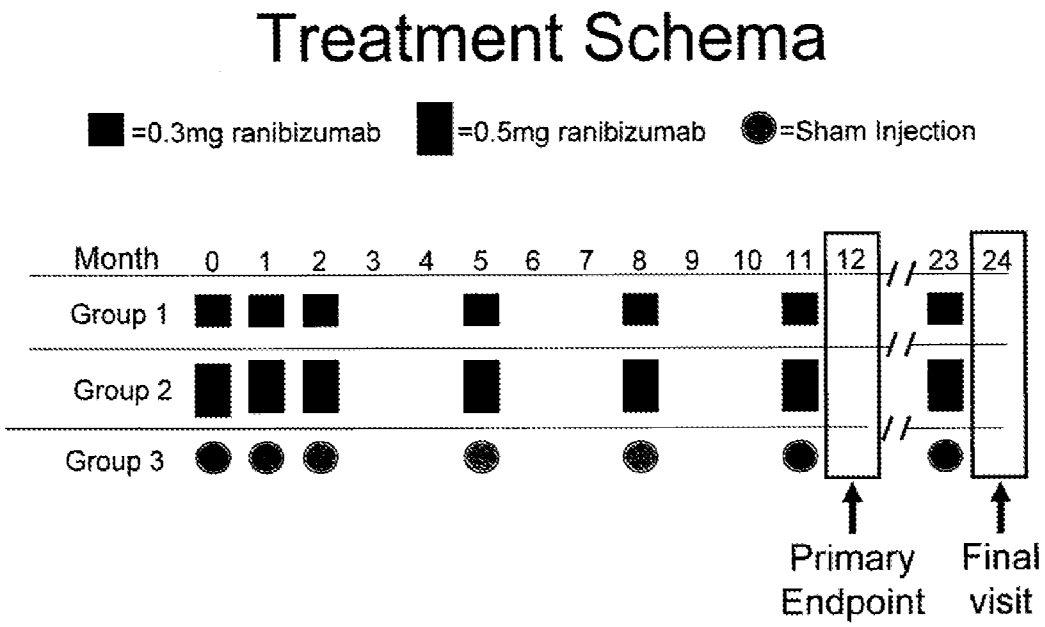


Figure 2

[71] Ex. 1004, Page 6, Lines 8-9.

[72] *Id.* at Page 31, Lines 8-13.

Figure 2 is annotated below to include the "first individual doses" and "second individual doses" terminology used by Shams.

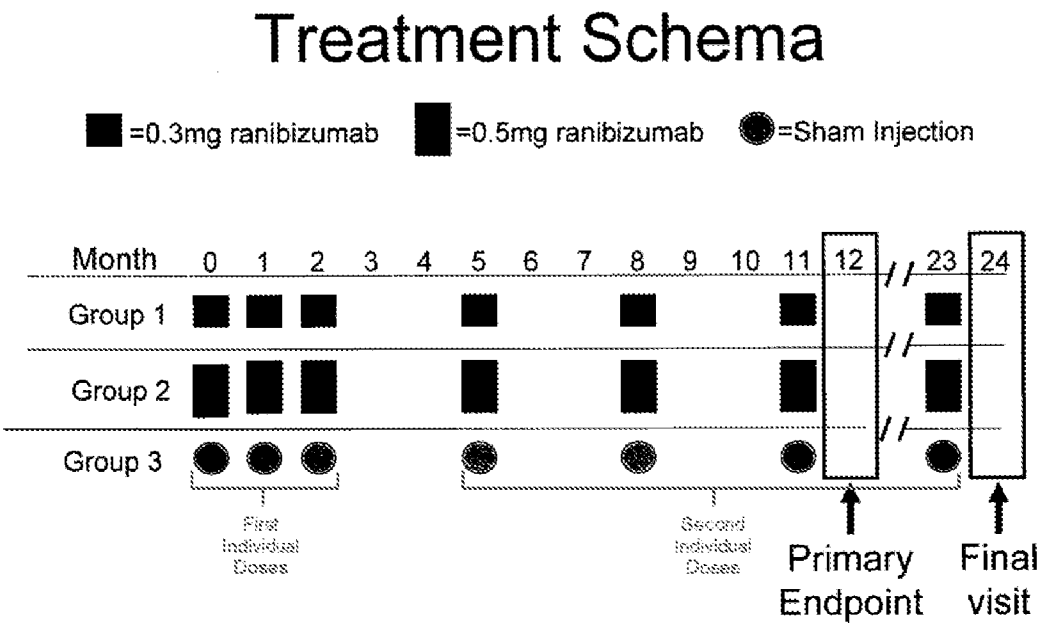


Figure 2

Using the '345 patent's terminology, Shams' "first individual doses" encompass initial doses (month 0) and secondary doses (months 1 and 2), and the application's "second individual doses" (months 5, 8, 11, . . .) are thus "tertiary doses."[73] The annotated Shams Figure 2 below illustrates the same regimen, but using the '345 patent's terminology.

[73] Ex. 1003 at ¶¶ 90-96.

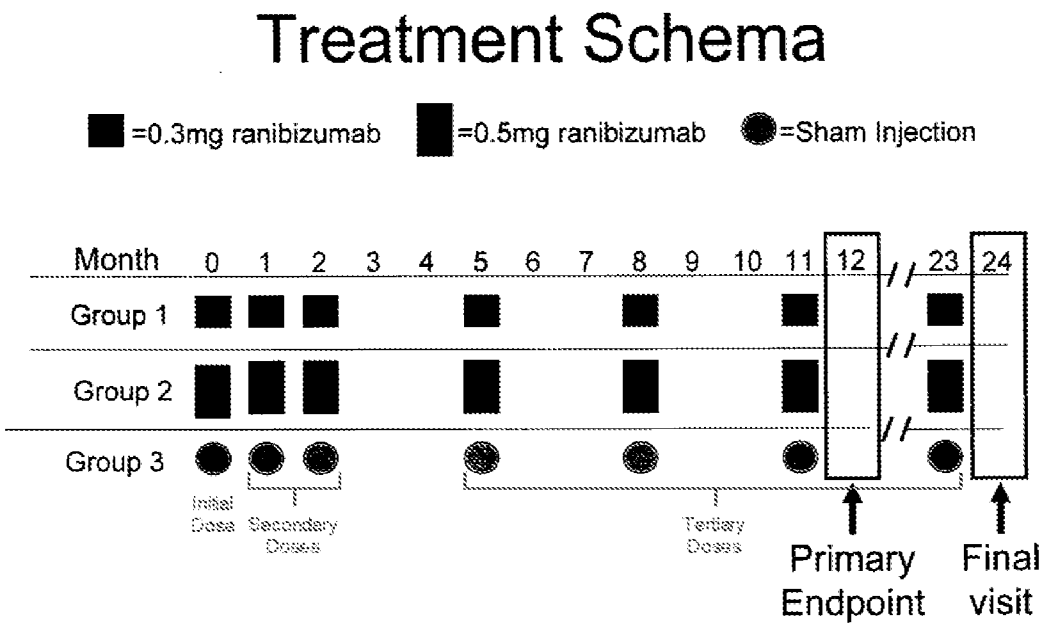


Figure 2

In addition to the '345 patent's purported discovery of less frequent dosing and its "initial, secondary, and tertiary" dosing regimen, Shams discloses claim 1's specific dosing frequency of "each secondary dose is administered 4 weeks after the immediately preceding dose" and "each tertiary dose is administered 12 weeks after the immediately preceding dose:" "In one embodiment of the invention, the first individual doses are administered at one month intervals (e.g., about 3 individual doses). The second [individual] dose is administered less frequently, e.g., at three month intervals (e.g., about 6 individual doses)."[74] This dosing frequency is illustrated in Figure 2.

[74] Ex. 1004, Page 23, Lines 16-18.

In addition to teaching the limitations of claim 1, Shams also discloses the limitations of claim 2 (specific drug administered), claims 3 and 4 (modes of administration), claim 5-7 (dose amounts), and claims 8-11 (disorders treated).

2. Claim 1

a) Shams discloses a "method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient"

Shams' "Summary of Invention" describes:[75]

> Methods for *treating intraocular neovascular disease* are provided. For example, methods include *administering to a mammal* a number of *first individual doses* of a VEGF antagonist, followed by *administering* to the mammal *a number of second individual doses* of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses.

Shams' "intraocular neovascular disease" meets claim 1's "angiogenic eye disorder."[76] "Administering to a mammal"[77] discloses the claimed "administering

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[75] *Id.* Page 4, Line 31-Page 5, Line 2 (emphasis added).

[76] Ex. 1003 at ¶ 88 (observing that the '345 patents lists, under "angiogenic disorders," disorders that Shams lists as "intraocular neovascular diseases").

[77] Shams describes "human patients" as preferred examples of "mammals." *See* Ex. 1004 at Page 23, Lines 30-34 ("Another aspect of the invention is the treatment

to the patient."[78] "Sequentially administering" is taught by Shams' "administering a number of first individual doses . . . followed by administering . . . a number of second individual doses."[79] Shams' administration meets the '345 patent's definition of "sequentially administered:" "each dose of VEGF antagonist is administered to the patient at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months)."[80]

b) Shams discloses the claimed initial dose of VEGF

Shams discloses claim 1's "single initial dose of a VEGF antagonist." The '345 patent defines an "initial dose" as "the dose which is administered at the beginning of the treatment regimen (also referred to as the 'baseline dose')."[81] The initial dose of the "number of first individual doses" in Shams (*see* annotated

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of an intraocular neovascular disease, e.g., wet form AMD, by administering to a mammal, preferably a human patient, a number of first individual doses of a compound, e.g., a VEGF antagonist, followed by administering a number of second individual doses of the compound.")

[78] Ex. 1003 at ¶ 88.

[79] *Id.* at ¶ 89.

[80] Ex. 1001, Col. 3:32-36.

[81] *Id.* at Col. 3:44-46.

Figure 2 below) corresponds to the claimed "single initial dose of a VEGF antagonist."

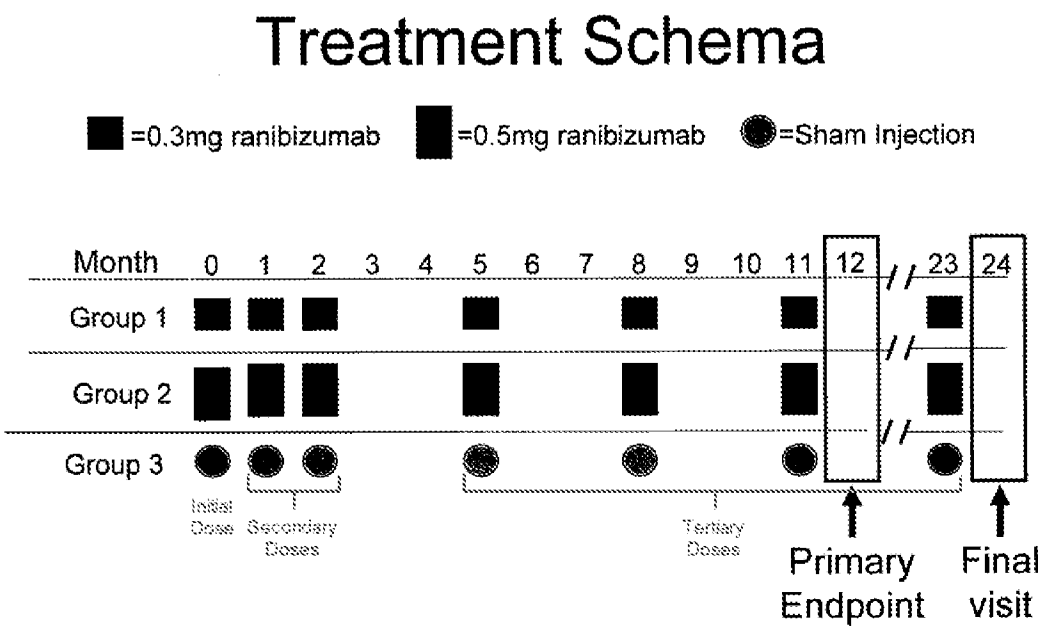

Figure 2

Shams discloses "wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component." Shams describes VEGF antagonist as including "VEGF-Trap (Regeneron)."[82] One of skill in the art would understand that "VEGF Trap (Regeneron)" includes Regeneron's fusion protein, which, in 2006, included "a receptor-based chimeric molecule comprising an immunoglobin-like (Ig)

[82] Ex. 1004, Page 6, Line 27 – Page 7, Line 6.

domain 2 of a first VEGF receptor which is Fltl and lg domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component."[83] Consistent with its description of specific VEGF antagonists applicable to the 4+12 week dosing regimen, Shams teaches that "[a]ny compound which binds to VEGF or a VEGF receptor and reduces the severity of symptoms or conditions associated with an intraocular neovascular disease may be used in this embodiment of the invention."[84] Regeneron's VEGF Trap binds to VEGF receptors to hinder VEGF interaction and interfere with the normal biological activity of VEGF.[85]

c) Shams discloses the claimed "followed by one or more secondary doses of the VEGF antagonist . . . wherein each secondary dose is administered 4 weeks after the immediately preceding dose"

The '345 patent defines "secondary dose" as "the doses which are administered after the initial dose."[86] Shams discloses doses administered after the

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[83] Ex. 1003 at ¶ 89.

[84] Ex. 1004, Page 26, Lines 6-8; *see also id.* at Page 22, Lines 15-18 ("The term "therapeutic" in this context means that the compounds binds to the ligand, VEGF, and produce a change in the symptoms or conditions associated with the disease or condition which is being treated.")

[85] Ex. 1001, Col. 4:48-60.

[86] *Id.* at Col. 3:46-48.

initial dose; for example, in Figure 2, the initial dose is followed by a second dose and a third dose.

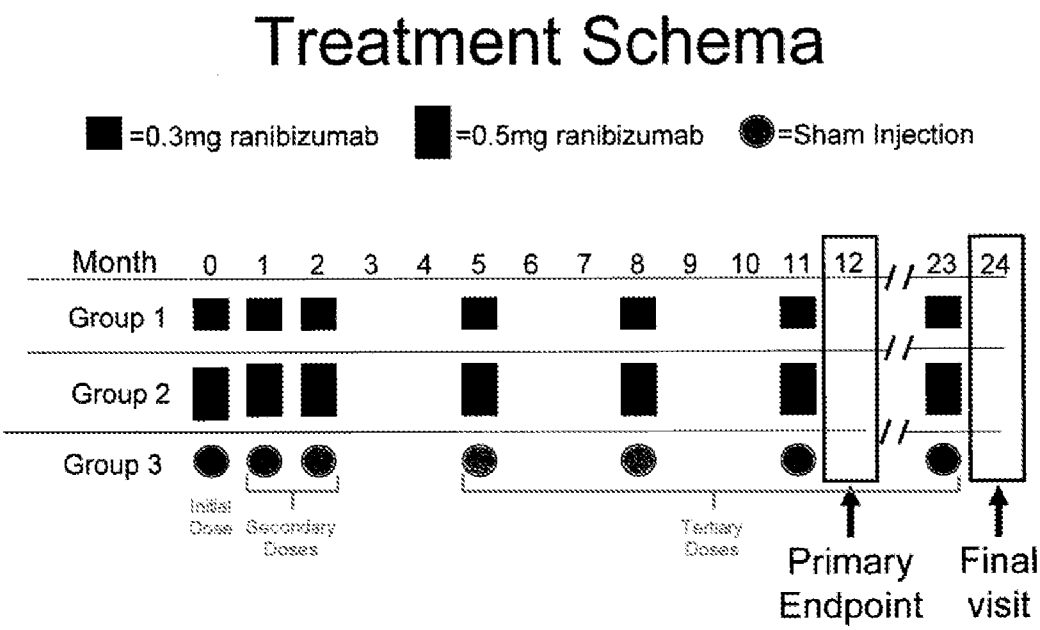

Figure 2

The second and third doses are thus "secondary doses," as defined by the '345 patent.

Further, Shams discloses that the one or more secondary doses of VEGF antagonist are "administered 4 weeks after the immediately preceding dose." For example, Shams discloses "the first individual doses are administered at one month intervals (e.g., about 3 individual doses),"[87] which are illustrated in Shams' Figure 2 (annotated above).

[87] Ex. 1004, Page 23, Lines 16-17.

One of skill in the art would understand that Shams' "one month interval" dosing discloses claim 1's "4 week" dosing frequency for at least three separate reasons.[88] First, the '345 patent equates monthly dosing to 4 week dosing.[89] For instance, the '345 patent's examples are based on an equivalence between monthly dosing and 4 week dosing: "For purposes of the following Examples, 'monthly' dosing is equivalent to dosing once every four weeks."[90] The patent's specific discussion of Example 4 also equates monthly and 4 week dosing: "patients receiving VEGFT 2 mg monthly (2Q4) achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline."[91] "2Q4" is understood in the art to be shorthand for dosing "every 4 weeks"[92] and so the '345 patent's use of "monthly (2Q4)" would be understood to mean that "monthly" dosing is the same frequency as "every 4 weeks."[93] In Example 6, Regeneron

[88] Ex. 1003 at ¶¶ 92-94.

[89] *Id.* at ¶ 93.

[90] Ex. 1001, Col. 7:67-8:2.

[91] *Id.* at Col. 13:47-49.

[92] Ex. 1003 at ¶ 93; *see also* Ex. 1004, Page 22:31-32 (describing a sequence of "weekly, biweekly, and monthly" dosing).

[93] Ex. 1003 at ¶ 93.

describes a study where "patients received 6 monthly injections," and then described those injections as administered "once every four weeks from Week 0 through Week 20."[94] Thus, the '345 patent, in the paragraph describing Example 6, uses the terms interchangeably. [95] In Example 7, Regeneron described a "dosing regimen within the scope of the present invention" as including VEGF Trap "administered by intravitreal injection once every 4 weeks (monthly).[96] Once again, the '345 patent discloses that "4 weeks" and "monthly" are to be used interchangeably.[97]

Second, it is common in the art to use "one month dosing" and "4 week dosing" interchangeably.[98] Typically, surgeons and patients calendar follow-up treatments on a weekly basis (i.e., the same day (and time) of a following week), instead of returning on the same date in a future month. [99] In those cases, returning "monthly" is understood to mean returning in 4 weeks on the same day of the

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[94] Ex. 1001 at Col. 14:59-66.

[95] Ex. 1003 at ¶ 93.

[96] Ex. 1001 at Col. 15:40-41.

[97] Ex. 1003 at ¶ 93.

[98] *Id.* at ¶ 92.

[99] *Id.*

week.[100] Additionally, many surgeons have practices in different locations and visit a specific office on the same days every week.[101] In such instances, the surgeon and patient may arrange a one-month "follow-up" but imply meeting on the same day in a future week.[102]

Third, Regeneron has frequently equated monthly and 4–week dosing.[103] For example, Heier (which Patent Owner cited as evidence of "unexpected results" during prosecution[104]) equates monthly with 4 week dosing: "Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4)."[105] In a different Heier publication, Regeneron stated that

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[100] *Id.*

[101] *Id.*

[102] *Id.*

[103] *Id.* at ¶ 94.

[104] Ex. 1002, Response, 06/28/2019, Page 8.

[105] Ex. 1012, Page 2538, "Intervention." *See also id.* at 2546 ("all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug ("[A]ll patients were

"During the 12–week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses."[106]

d) Shams discloses the claimed "followed by one or more tertiary doses of the VEGF antagonist . . . each tertiary dose is administered 12 weeks after the immediately preceding dose"

Shams discloses the secondary dose(s) "followed by one or more tertiary doses of the VEGF antagonist." The '345 patent defines "tertiary dose" as "the doses which are administered after the secondary doses."[107] Shams' "second individual doses" are administered after the "first individual doses" (which correspond to the claimed "secondary doses"), and, thus, the second individual doses are the claimed "tertiary doses."[108]

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monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections).").

[106] Ex. 1013 at 1110, Legend for Figure 2.

[107] Ex. 1001, Col. 3:48-49.

[108] Ex. 1003 at ¶¶ 95-96.

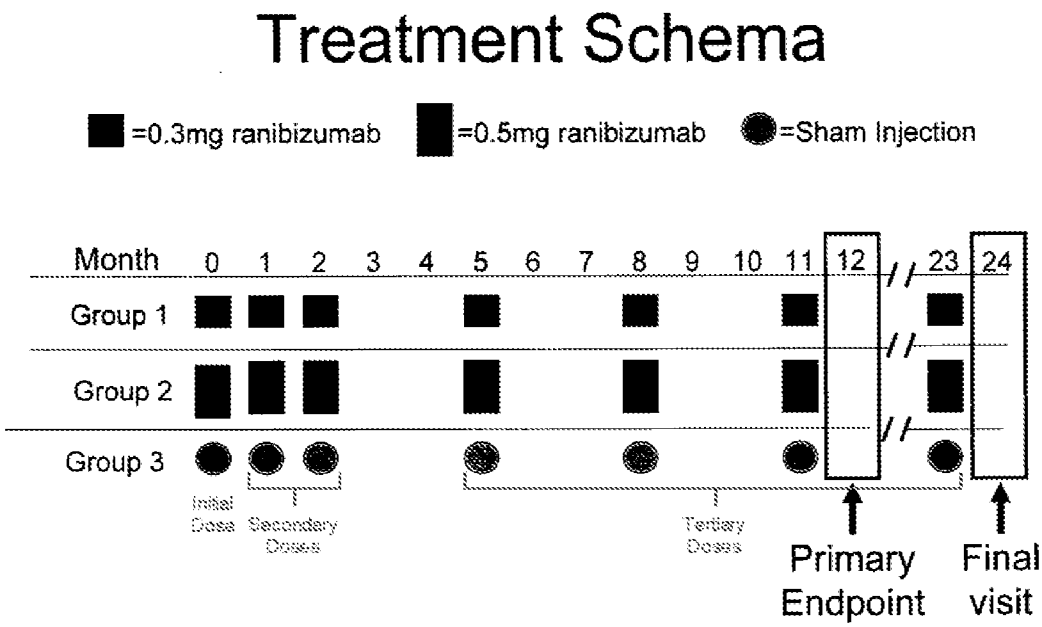

Figure 2

Further, Shams discloses that the tertiary "doses are administered at three month intervals (e.g., about 6 individual doses)."[109] One of skill in the art would understand that a three month dosing frequency discloses the claimed "12 week" dosing.[110] As explained above, one of skill in the art would equate monthly dosing with a 4–week frequency, evidenced by the '345 patent's specification and Regeneron's prosecution arguments. One of skill in the art would further understand "3 month" dosing to be equivalent to a 12–week frequency. [111]

[109] Ex. 1004, Page 5, Lines 23-24

[110] Ex. 1003 at ¶ 97.

[111] *Id.*

Surgeons frequently refer to 12–week dosing as "three month" dosing or "quarterly" dosing.[112] Consistently, a 2011 Regeneron publication equated "4 week" with "monthly" dosing and equated "12–week" with "quarterly" dosing when describing the results of Regeneron's Phase 2 study: "During the 12–week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses; those in the quarterly dosing groups received 0.5, 2, or 4 mg of VEGF Trap-Eye every 12 weeks on day 0 and at week 12 for a total of 2 doses."[113] Thus, Shams discloses "each tertiary dose is administered 12 weeks after the immediately preceding dose."

3. Dependent claims

a) Claim 2: Shams discloses the claimed drug

Shams discloses that the "VEGF antagonist" includes "VEGF Trap (Regeneron)."[114] Shams also discloses that the VEGF antagonist treats eye

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[112] *Id.*

[113] Ex. 1013 at 1110, Legend for Figure 2 (emphasis added).

[114] Ex. 1003 at ¶ 99.

disorders,[115] which would lead one of skill in the art to understand that "VEGF Trap (Regeneron)" refers to Regeneron's VEGF Trap treatment for eye disorders.[116] "Aflibercept" is another name for Regeneron's VEGF Trap treatment for eye disorders.[117] Shams thus discloses "wherein the VEGF antagonist is aflibercept."

b) Claims 3 and 4: Shams discloses the claimed modes of administration

Shams discloses "wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration" (claim 3), and "the intraocular administration is intravitreal administration" (claim 4). [118] For example, Shams discloses "[t]he therapeutic compound for treatment of an intraocular neovascular disease is typically administered by ocular, intraocular, and/or intravitreal injection."[119]

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[115] *E.g.*, Ex. 1004 at Title ("Method for Treating Intraocular Neovascular Diseases").

[116] Ex. 1003 at ¶ 99.

[117] *Id.*

[118] *Id.* at ¶ 98.

[119] Ex. 1004, Page 25, Lines 15-16.

c) Claims 5-7: Shams discloses the claimed dose amounts

Shams explicitly discloses "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist" (claim 5) and "wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist" (claim 6). [120] For example, Shams discloses administering a 0.5 mg dose.[121] Further, Shams discloses a range (0.1 mg – 20 mg)[122] which covers the range of claim 5 (0.5 mg – 2.0 mg), the dose of claim 6 (0.5 mg), and the dose of claim 7 (2.0 mg).

d) Claims 8-11: Shams discloses the disorders treated

Shams discloses "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" (claim 8), "wherein the angiogenic eye disorder is age related macular degeneration" (claim 9), "wherein the angiogenic eye disorder is diabetic retinopathy" (claim 10), and "wherein the angiogenic eye

[120] Ex. 1003 at ¶ 101.

[121] *See, e.g.*, Ex. 1004 at Figure 2; Page 31, Lines 8-9.

[122] Ex. 1004, Page 24, Lines 18-20.

disorder is diabetic macular edema" (claim 11). [123] For example, Shams lists various "intraocular neovascular disease[s]" treatable by the disclosed VEGF antagonists, including "age-related macular degeneration (AMD), diabetic and other ischemia-related retinopathies, diabetic macular edema." [124]

B. Ground 2: The '345 Patent's Claims Are Rendered Obvious by the 2009 Press Release in view of Shams

1. The 2009 Press Release

The 2009 Press Release published September 14, 2009, more than one year before the '345 patent's earliest priority date, and thus is prior art to the '345 patent under 35 U.S.C. §§ 102(a)(1) and (2).[125] The 2009 Press Release teaches, among other arms, "that patients received intravitreal doses of 0.5 mg or 2g VEGF Tap-Eye [sic] at 4–week intervals in the first year, followed by continual treatment for another year on a flexible, PRN regiment, with a dose administered at least every 12 weeks."[126] The PTO cited this teaching in rejecting the '345 patent as anticipated by the 2009 Press Release. To overcome the 2009 Press Release, Regeneron argued that as-needed tertiary dosing between 4 and 12 weeks does not

[123] Ex. 1003 at ¶ 102.

[124] Ex. 1004, Page 21, Lines 1-6.

[125] Ex. 1005.

[126] *Id.*

explicitly disclose a tertiary 12–week dosing frequency component because "[a] practitioner of ordinary skill in the art would not have understood a PRN dosing regimen with 4 and 12–week limits as encompassing a [12–week dosing] regimen."[127] Regeneron also argued that the claims were not inherently disclosed in the Press Release because "[t]hough the Press Release discussed a PRN dosing regimen wherein a dose interval may extend out as far as 12 weeks, the dosages administered to patients were not necessarily this infrequent. For this reason, the Press Release was insufficient as an inherently anticipating reference."[128]

An examiner interview followed on March 6, 2020.[129] Later that month, Regeneron filed a supplemental response presenting more arguments to distinguish claims 32-42 (issued claims 1-11) from the 2009 Press Release:[130]

> Claims 32-42 relate to a method requiring tertiary dosing administered 12 weeks after the immediately preceding dose. There is a single appearance of the words "12 weeks" within the fourth paragraph of the Press Release. However, this paragraph is referring to a "flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more

[127] Ex. 1002, Response, 01/23/2020, Pages 6-8.

[128] *Id.* (emphasis in original).

[129] Ex. 1002, Response, 03/16/2020, Page 4.

[130] *Id.*

> often than every four weeks". As explained in our January 23, 2020 Response, this is not a disclosure of a regimen having 12–week tertiary dosing as specified in the claims. Mere mention of a prospective possibility of dosing at 12 weeks does not specifically indicate or teach towards a method where 12–week dosing would be undertaken, let alone successful.

The Examiner explicitly relied on Regeneron's arguments that the 2009 Press Release did not teach or suggest 12–week tertiary dosing.

This petition adds Shams to provide the 12–week tertiary dosing allegedly absent from the 2009 Press Release. Specifically, this petition relies on a different teaching in the Press Release than that relied upon by the PTO, a tertiary 8–week dosing regimen, and combines with Shams' teachings of 12-week tertiary dosing.

2. Claim 1

a) The 2009 Press Release teaches a "method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient"

The 2009 Press Release teaches a "method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient." The 2009 Press Release announced "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular

degeneration (wet AMD)."[131] The 2009 Press Release explains: "In the first year of the studies, the safety and efficacy of VEGF Trap-Eye at doses of 0.5 mg and 2.0 mg administered at four week intervals and 2.0 mg at an eight-week dosing interval following one additional 2.0 mg dose at week four are being evaluated."[132] The 2009 Press Release also describes a "development for the treatment of [DME]" where VEGF Trap-Eye is dosed at 0.5 mg or 2.0 mg monthly, 2 mg on an as-needed basis after three monthly loading doses, or 2 mg every eight weeks after three monthly loading doses.[133] This disclosure in the 2009 Press Release corresponds to the '345 patent's Examples 4 and 5[134] and teaches a "method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient."[135]

b) The 2009 Press Release teaches the claimed initial dose of VEGF

The 2009 Press Release teaches "a single initial dose of a VEGF antagonist." The 2009 Press Release teaches two studies with 8–week tertiary dosing, both of

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[131] Ex. 1005, Title.

[132] *Id.* at 1, Fourth Paragraph.

[133] *Id.* at 2, Second Paragraph.

[134] Ex. 1003 at ¶¶ 77-78.

[135] *Id.* at ¶ 106.

which include an "initial dose." First, the Press Release teaches: "In the first year of the studies, the safety and efficacy of VEGF Trap-Eye at doses of 0.5 mg and 2.0 mg administered at four week intervals and 2.0 mg at an eight-week dosing interval following one additional 2.0 mg dose at week four are being evaluated." Second, the 2009 Press Release teaches: "VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses." The first dose in each of these arms corresponds to the claimed "single initial dose."[136]

The 2009 Press Release teaches "wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component." The 2009 Press Release describes studies related to VEGF Trap-Eye, which one of skill in the art would understand includes "a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component." [137]

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[136] *Id.* at ¶ 106.

[137] *Id.* at ¶ 105.

c) The 2009 Press Release teaches the claimed "one or more secondary doses"

The 2009 Press Release teaches the initial dose "followed by one or more secondary doses of the VEGF antagonist . . . wherein each secondary dose is administered 4 weeks after the immediately preceding dose."[138] In one study, the 2009 Press Release teaches an initial dose of 2.0 mg and "one additional 2.0 mg dose at week four." In other words, the 2009 Press Release teaches a secondary dose of VEGF Trap-Eye at week four, i.e., "administered 4 weeks after the immediately preceding dose." In another study, the 2009 Press Release teaches that after an initial dose of 2.0 mg, two additional "monthly loading doses" are administered. In other words, the 2009 Press Release teaches two secondary doses of VEGF Trap-Eye at weeks four and eight, i.e., "administered 4 weeks after the immediately preceding dose."

d) The 2009 Press Release in view of Shams teaches the claimed "one or more tertiary doses"

The 2009 Press Release teaches the secondary dose(s) "followed by one or more tertiary doses of the VEGF antagonist."[139] In the first study, the 2009 Press Release teaches 8–week tertiary doses of VEGF Trap-Eye following the week four

[138] *Id.* at ¶ 107.

[139] *Id.* at ¶ 108.

dose and, in the second, the press release teaches 8–week tertiary dosing teaches following the three monthly loading doses. Thus, the 2009 Press Release teaches "one or more tertiary doses."

The 2009 Press Release's 8–week tertiary doses do not meet "each tertiary dose is administered 12 weeks after the immediately preceding dose." Shams teaches an effective treatment of "intraocular neovascular disease" with tertiary doses every three months.[140] It would have been natural for one of skill in the art to look at Shams' teachings when considering the 2009 Press Release's 4 + 8 week dosing: (1) Shams was assigned to Genentech, who was a research leader in the early stages of VEGF antagonist treatment; (2) Regeneron's clinical trials use Genentech's ranibizumab as the control dose; and (3) Shams lists Regeneron's VEGF Trap as a suitable antagonist for its 12 week tertiary dosing program.[141]

One of skill in the art would have been motivated at least by market forces to extend the 2009 Press Release's 8–week tertiary dosing. As recognized in the 2009 Press Release, "monthly office visits and examinations . . . are inconvenient for these often elderly patients."[142] The inconvenience included the physical

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[140] *E.g.*, Ex. 1004, Page 23, Lines 9-11.

[141] Ex. 1003 at ¶ 112.

[142] Ex. 1005 at 1, Third Paragraph.

discomfort of an intraocular injection and the mobility limitations of some elderly patients.[143] The monthly injections also inconvenienced retinal specialists because their practices could quickly fill with monthly maintenance injections.[144] Also, the high price ($2,000 per injection) of Lucentis was a significant market force that drove longer tertiary dosing.[145]

Thus, claim 1 is nothing more that the simple substitution of Shams' 12–week tertiary dose for the 2009 Press Release's 8–week tertiary dose.[146] Similarly, the known work by Genentech (12–week tertiary dosing) would prompt variations in the 2009 Press Release for at least the reason that market forces provided an incentive to extend the 8–week tertiary dosing. [147] Further, the modification merely combines prior art elements (Shams' 12–week tertiary dosing) to a known method (the 2009 Press Release's 4–week secondary dosing plus 12–week tertiary dosing) to arrive at a predicate result (a successful treatment of angiogenic eye disorders). The success was predictable because Shams teaches a successful 4 +

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[143] Ex. 1003 at ¶ 110.

[144] *Id.*

[145] *Id.*

[146] *Id.* at 115.

[147] *Id.* at 111-12.

12 week dosing program, and also because Regeneron publically announced that VEGF Trap was successful in quarterly doses.[148]

Thus, the 2009 Press Release in view of Shams renders obvious "each tertiary dose is administered 12 weeks after the immediately preceding dose."

3. Dependent claims

a) Claim 2: The 2009 Press Release and Shams teach the claimed drug

The 2009 Press Release in view of Shams teaches "wherein the VEGF antagonist is aflibercept." The 2009 Press Release describes studies related to VEGF Trap-Eye, which is also called "aflibercept."[149]

b) Claims 3 and 4: The 2009 Press Release and Shams teach the claimed modes of administration

The 2009 Press Release in view of Shams teaches "wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration" (claim 3) and "the intraocular administration is intravitreal administration" (claim 4).[150] For example, the 2009 Press Release teaches: "In each study of the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) program,

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[148] Ex. 1003 at ¶ 114 (citing Regeneron SEC Form 10-Q (May 4, 2007) at 17-18).

[149] Ex. 1003 at ¶ 116.

[150] *Id.* at 117.

VEGF Trap-Eye is being evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection."[151] Shams teaches "[t]he therapeutic compound for treatment of an intraocular neovascular disease is typically administered by ocular, intraocular, and/or intravitreal injection."[152]

c) Claims 5-7: The 2009 Press Release and Shams teach the claimed dose amounts

The 2009 Press Release in view of Shams teaches "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist" (claim 5), "wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist" (claim 6), and "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist" (claim 7).[153] For example, the 2009 Press Release teaches: "In the first year of the studies, the safety and efficacy of VEGF Trap-Eye at doses of 0.5 mg and 2.0 mg administered at four week intervals and 2.0 mg at an eight-week dosing interval following one additional 2.0 mg dose at week four are being evaluated" and "VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly

[151] Ex. 1005 at 1, First Paragraph.

[152] Ex. 1004, Page 25, Lines 15-16.

[153] Ex. 1003 at ¶ 118.

loading doses."[154] Shams also teaches administering the claimed doses (*see* Ground 1 above). Thus, the 2009 Press Release in view of Shams teaches the specific dosing regimens of claims 5-7.

d) Claims 8-11: The 2009 Press Release and Shams teach the disorders treated

The 2009 Press Release in view of Shams teaches "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" (claim 8), "wherein the angiogenic eye disorder is age related macular degeneration" (claim 9), "wherein the angiogenic eye disorder is diabetic retinopathy" (claim 10), and "wherein the angiogenic eye disorder is diabetic macular edema" (claim 11).[155] For example, the 2009 Press Release teaches "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD),"[156] and "VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME)."[157] Shams provides

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[154] Ex. 1015 at 1, Fourth Paragraph and 2, Second Paragraph.

[155] Ex. 1003 at ¶ 119.

[156] Ex. 1015 at 1, First Paragraph.

[157] *Id.* at 2, Second Paragraph.

examples of "intraocular neovascular disease[s]" treatable by the disclosed VEGF antagonists, including "age-related macular degeneration (AMD), diabetic and other ischemia-related retinopathies, diabetic macular edema." [158]

VIII. GROUND 3: CLAIMS 1-11 FAIL TO SATISFY THE WRITTEN DESCRIPTION REQUIREMENT

Petitioner respectfully requests the Board cancel all claims of the '345 patent on the following Ground 3: Claims 1-11 fail the written description under pre-AIA 35 U.S.C. § 112, first paragraph and post-AIA 35 U.S.C. § 112(a).

The '345 patent fails to show Patent Owner's possession for all claims because the dosing regimen required by claim 1 is not supported. "'The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009) (quoting *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003)). "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (citing

[158] Ex. 1004, Page 21, Lines 1-6.

Fujikawa v. Wattanasin, 93 F.3d 1559, 1570 (Fed. Cir. 1996)). "Nonetheless, the disclosure 'must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention.'" *Purdue*, 230 F.3d at 1323 (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2D (BNA) 1111, 1117 (Fed. Cir. 1991) (alteration in original)).

The '345 patent fails to show possession of a dosing regimen with initial, secondary, and tertiary dosing where "each secondary dose is administered 4 weeks after the immediately preceding dose," and "each tertiary dose is administered 12 weeks after the immediately preceding dose" as required by all claims. "12 week" tertiary dosing is mentioned in two places in the '345 patent, but neither provides support for the claimed 4 week secondary doses and 12 week tertiary doses. The '345 patent's "Dosing Regimens" section lists myriad combinations of secondary and tertiary dosing and does not differentiate 4 week secondary dosing followed by 12–week tertiary dosing. Example 4 describes PRN tertiary dosing with an upper limit of 12 weeks, which Regeneron labelled insufficient during prosecution. Neither provides support for the claimed 4–week plus 12–week dosing regimen.

A. The '345 Patent's Disclosure of 12–Week Dosing

The '345 patent has little discussion of 12–week tertiary dosing. The "Brief Summary" discusses tertiary doses, but it characterizes the inventor's discovery

broadly as tertiary dosing "once every 8 or more weeks."[159] The sole figure in the '345 patent describes tertiary dosing, but it is a fixed 8–week dosing regimen: "In this regimen, a single 'initial dose' of [VEGFT] is administered at the beginning of the treatment regimen (i.e. at 'week 0'), two 'secondary doses' are administered at weeks 4 and 8, respectively, and at least six 'tertiary doses' are administered once every 8 weeks thereafter."[160]

When a 12–week tertiary dose is mentioned, the '345 patent includes it as one of 14 "or more" possible tertiary dosing frequencies: [161]

> In one exemplary embodiment of the present invention, each secondary dose is administered 2 to 4 (e.g., 2, 2½, 3, 3½, or 4) weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, **12**, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose.

This range has only one limit; the tertiary doses must be "at least 8 weeks." There is no upper bound on the range. Further, this disclosure is not limited to "each secondary dose is administered 4 weeks after the immediately preceding dose,"

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[159] Ex. 1001, Col. 2:16.

[160] *Id.* at Col. 2:64-3:2.

[161] *Id.* at Col. 3:57-62.

and "each tertiary dose is administered 12 weeks after the immediately preceding dose," as required by claim 1. Combinations of different tertiary doses, for example, are included in the scope of this description—the '345 patent explains that "each tertiary dose may be administered at the same frequency as the other tertiary doses" or, alternatively, the frequency at which "tertiary disease are administered to a patient can vary over the course of the treatment regimen."[162]

When the '345 patent next mentions a 12–week dose frequency, the tertiary 12–week dose(s) is preceded by four 8–week "tertiary doses" and 12 weeks is again only one choice, among many, for the tertiary dose: [163]

> [E]ach secondary dose may be administered to the patient 4 weeks after the immediately preceding dose. . . . [F]ollowed by at least 5 tertiary doses of the VEGF antagonist, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered from 8 to **12** (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, **12**) weeks after the immediately preceding dose. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

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[162] *Id.* at Col. 4:23-34.

[163] *Id.* at Col. 23-43 (emphasis added).

Because the tertiary dosing in this description includes 8–week dosing followed by 12–week dosing, it does not describe "each tertiary dose is administered 12 weeks after the immediately preceding dose."[164]

The remainder of the '345 patent includes no discussion of a dosing regimen where "each tertiary dose is administered 12 weeks after the immediately preceding dose." After the "Dosing Regimens" section, the patent continues with listing VEGF antagonists,[165] angiogenic eye disorders,[166] pharmaceutical formulations,[167] modes of administration, [168] VEGF dosing amounts, [169] and

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[164] This discussion in the '345 patent corresponds to Claim 5 of the parent PCT Application. That claim does not teach "sequentially administering" secondary doses and tertiary doses of the same frequency for the same reasons as the corresponding paragraph in the '345 patent.

[165] Ex. 1001, Col. 4:47-5:20.

[166] *Id.* at Col. 5:21-39.

[167] *Id.* at Col. 5:40-6:7.

[168] *Id.* at Col. 6:8-24.

[169] *Id.* at Col. 6:25-7:25.

treatment population and efficacy.[170] These sections do not mention 12–week dosing frequencies.

The patent then describes seven examples. Examples 1 and 2 correspond to Regeneron's Phase 1 and 2 Aflibercept trials (described in Regeneron's 2006 and 2007 press releases[171]) and do not include any tertiary dosing.[172] Example 3 describes a Phase 1 trial of a single dose, and similarly does not include any tertiary dosing.[173] Example 4 corresponds to the Phase 3 clinical trial (described in Regeneron's 2009 Press Release[174]) and describes tertiary dosing, including an 8–week fixed tertiary dose and PRN tertiary dosing with a maximum of 12–weeks; this cannot provide support for the claimed dosing regimen because Regeneron argued during prosecution that the Press Release's identical disclosure does not teach "each tertiary dose is administered 12 weeks after the immediately preceding dose."[175] Example 5 corresponds to a Phase 2 clinical trial in diabetic macular

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[170] *Id.* at Col. 7:26-44.

[171] Ex. 1003 at ¶¶ 74-75.

[172] *Id.* at ¶ 76.

[173] *Id.*.

[174] *Id.* at ¶ 77.

[175] Ex. 1002, Response, 03/16/2020, Pages 4-5.

edema, respectively, and, like Example 4, describes tertiary dosing but is limited to administering each tertiary dose 8 weeks after the immediately preceding dose. Example 6 describes a Phase 3 dosing study in central retinal vein occlusion and does not include any tertiary dosing. Example 7 lists 20 "examples of dosing regimens within the scope of the present invention."[176] Although Example 7 discloses tertiary dosing, the dosing frequency is described as either "once every 8 weeks," "less frequent" than the secondary dosing, or PRN.[177] None of the 20 exemplary dosing regimens provided in Example 7 include a 12–week tertiary dose.[178]

B. Regeneron's Discussion of 12–week Dosing During Prosecution

Regeneron overcame a double patenting rejection by arguing, in part, that the '345 patent was non-obvious over Patent Owner's earlier patents.[179] Specifically, Regeneron argued that the "standard of care for the treatment of [AMD] was to administer an antibody formulation (ranibizumab) by injection to

[176] Ex. 1003 at ¶ 80.

[177] *Id.*

[178] *Id.*

[179] Ex. 1002, Response, 06/28/2019.

the eye once per month"[180] and characterized a paper by Heier[181] as "showing improved unexpected results" that supports nonobviousness of the claimed 12–week tertiary dosing.[182] According to Patent Owner, "the PRN treatment protocol [disclosed in Heier] as encompassed by . . . the 12–week dosing of claim [1] achieves results which would be surprisingly as good or better than the results obtained with monthly treatment."[183] Equating Heier with claim 1, Regeneron stated that "the Heier *et al.* results suggest that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent [claim 1], it is possible to treat angiogenic eye disorder…on a less frequent basis than previously thought possible."[184]

Heier published in December 2012 and describes a study to determine effect on "neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection . . . with monthly

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[180] *Id.*

[181] *Id.*

[182] Ex. 1002, Response, 06/28/2019 (citing 1012.)

[183] *Id.* at 9.

[184] *Id.*

ranibizumab."[185] Heier states that all patients "received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections."[186] As Regeneron indicated, Heier teaches the same regimen as Example 4 of the '345 patent.[187]

In the next action, the PTO withdrew the double patenting rejection and added a rejection of (now) claims 1-11 as anticipated by the 2009 Press Release.[188] The PTO correctly described the Press Release as "teach[ing] that patients received/intravitreal doses of 0.5 mg or 2g VEGF Tap-Eye [sic] at 4–week intervals in the first year, followed by continual treatment for another year on a flexible, PRN regiment, with a dose administered at least every 12 weeks."[189] The 2009 Press Release has essentially the same description as Heier, the journal article that Regeneron relied on to overcome the double patenting rejection, and Example 4 of the '345 patent.

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[185] Ex. 1012 at 2537.

[186] *Id.* at 246.

[187] Ex. 1002, Response, 06/28/2019, Page 8.

[188] Ex. 1002, Rejection, 10/01/2019, Pages 4-5.

[189] *Id.*

In response to the 2009 Press Release, Regeneron changed its characterization of 12–week dosing regimens, now arguing that as-needed tertiary dosing between 4 and 12 weeks does not explicitly disclose a tertiary 12–week dosing frequency component because "[a] practitioner of ordinary skill in the art would not have understood a PRN dosing regimen with 4 and 12–week limits as encompassing a [12–week dosing] regimen. [190] Regeneron also argued that the claims were not inherently disclosed in the Press Release because "[t]hough the Press Release discussed a PRN dosing regimen wherein a dose interval may extend out as far as 12 weeks, the dosages administered to patients were not necessarily this infrequent. For this reason, the Press Release was insufficient as an inherently anticipating reference."[191] That exact dosing regimen is taught by Heier, the journal article that Regeneron cited to overcome the double patenting rejection by proving "unexpected results." Regeneron did not attempt to reconcile the inconsistency between its reliance on Heier (to overcome the first rejection) as sufficiently disclosing the claimed regimen to support unexpected results with its later critique of the 2009 Press Release as insufficient to disclose that same regimen.

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[190] Ex. 1002, Response, 01/23/2020, Pages 6-8.

[191] *Id.* (emphasis in original).

An examiner interview followed on March 6, 2020.[192] Later that month, Regeneron filed a supplemental response presenting more arguments to distinguish claims 32-42 (issued claims 1-11) from the 2009 Press Release:[193]

> Claims 32-42 relate to a method requiring tertiary dosing administered 12 weeks after the immediately preceding dose. There is a single appearance of the words "12 weeks" within the fourth paragraph of the Press Release. However, this paragraph is referring to a "flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks". As explained in our January 23, 2020 Response, this is not a disclosure of a regimen having 12–week tertiary dosing as specified in the claims. Mere mention of a prospective possibility of dosing at 12 weeks does not specifically indicate or teach towards a method where 12–week dosing would be undertaken, let alone successful.

The Examiner explicitly relied on this argument to allow claims 32-42,[194] which issued on November 10, 2020, as claims 1-11 of the '345 patent.[195]

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[192] Ex. 1002, Response, 03/16/2020, Page 4.

[193] *Id.*

[194] Ex. 1002, Notice of Allowance, 04/01/20, Pages 2-3.

[195] Ex. 1001, Cover Page.

C. The '345 Patent Lacks Written Description Support for the Same Reasons Regeneron Articulated in its Critique of the 2009 Press Release

Before the PTO, Regeneron argued that the 2009 Press Release's teaching (which corresponds to Example 4)[196] of 12–week tertiary dosing was insufficient to teach a 12–week dosing regimen: [197] "Mere mention of a prospective possibility of dosing at 12 weeks . . . does not specifically indicate or teach toward a method where 12–week dosing would be undertaken, let alone successful." [198] This reasoning also applies to claim 1 and demonstrates that the claim lacks written description support.

The 2009 Press Release states that "[a]fter the first year of treatment [of 4–week secondary doses], patients will continue to be followed and treated for another year on a flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks." Example 4 discloses the same regimen: "During the second year of the study, . . . [tertiary doses] may be given as frequently as every 4 weeks, but no less frequently

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[196] Ex. 1003 at ¶¶ 77-78.

[197] Ex. 1002, Response to Office Action 03/16/2020, Page 4.

[198] *Id.*

than every 12 weeks."[199] Given that the '345 patent and the 2009 Press Release disclose the same tertiary dosing possibilities, and that Regeneron critiqued the 2009 Press Release (to thereby obtain allowance of the '345 patent) as insufficient to teach a 12–week dosing regimen, the '345 patent's disclosure is also insufficient to teach "each tertiary dose is administered 12 weeks after the immediately preceding dose."

D. The '345 Patent's Undifferentiated Disclosure of Various Dosing Regimens Is Insufficient to Support a Claim to a Specific 4-Week Secondary and 12–Week Tertiary Dosing Regimen

In *Novozymes,* the Federal Circuit held that an "application's undifferentiated description" of a specific invention is insufficient unless the disclosure "provide[s] sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities towards the claimed" elements. 723 F.3d at 1346 (quoting *In re Ruschig*, 379 F.2d 990, 994-95 (C.C.P.A. 1967)). Thus, "one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000); *see also Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367 (Fed. Cir. 2011); *Fujikawa*, 93 F.3d at 1570-71.

[199]Ex. 1001, Col. 10:12-14.

In *Purdue Pharma*, the claims required a method of administering an opioid so that the patient had specific plasma concentrations of the opioid at specific times. 230 F.3d at 1324. The original application described seven examples of administering an opioid, two of which included the required concentrations at the required times. *Id.* at 1326. But all seven examples also described numerous other parameters related to administering the opioid. *Id.* And nothing in the application's description suggested to one skilled in the art that the later-claimed concentrations (added during prosecution) were "an important defining quality" for the invention. *Id.* at 1327. Rather, the patentees appeared to have simply "pick[ed] a characteristic possessed by" some examples in the original application—a "characteristic that is not discussed even in passing in the disclosure." *Id.* The court explained that this was "exactly the type of overreaching the written description requirement was designed to guard against." *Id.*

Like *Purdue Pharma*, claim 1 of the '345 patent is specific—a 4–week secondary dosing frequency followed by a 12–week tertiary dosing frequency. And like *Purdue Pharma*, the '345 patent "discloses a forest in the original application, and [Patent Owner] then later pick[ed] a tree out of the forest and [said] here is my invention." *Purdue Pharma*, 230 F.3d at 1326. The '345 patent mentions 12–week tertiary dosing, but does so in an unbounded range of dosing

frequencies, with the only limit being that each tertiary dose must be "at least 8 weeks" frequency: "each tertiary dose is administered at least 8 (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more)."[200] This disclosure is much broader than claim 1's required "each secondary dose is administered 4 weeks after the immediately preceding dose," and "each tertiary dose is administered 12 weeks after the immediately preceding dose." The '345 patent explicitly teaches that the different secondary and tertiary doses can be administered at the same or different frequencies.[201] The '345 patent's combinations of secondary (2, 2½, 3, 3½, or 4 weeks) and tertiary doses (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) therefore allows for secondary dosing at varying frequencies and tertiary dosing at varying frequencies, yielding unlimited combinations of secondary and tertiary dosing frequencies. For example, assume that a secondary/tertiary dosing regimen consisted of two secondary doses followed by three tertiary doses and that the '345 patent described just five possible secondary dose frequencies and 14 possible

[200] Ex. 1001, Col. 3:60-62.

[201] *Id.* at Col. 4:23-34.

tertiary dose frequencies (i.e., ignore the "or more" tertiary doses), the possible dosing regimens gives 68,000[202] possible combinations.

Prosecution of the '345 patent reinforces that that the number of treatment options is vast. In overcoming the double patenting rejection, Regeneron described the treatment options as "virtually infinite:"[203]

> There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month.

Because the '345 patent also discloses a "virtually infinite" number of undifferentiated dosing regimens, the specific regimen of claim 1 is not reasonably supported by the disclosure.

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[202] Five choices for each of the first two doses and 14 choices for each of the last three doses. 5x5x14x14x14=68,600.

[203] Ex. 1002, Response, 06/28/2019.

Even if the '345 patent's vast disclosure had been limited to secondary doses of the same frequency and tertiary doses of the same frequency (which it is not), the number of combinations are still too many for one of skill in the art to recognize possession of the specific invention. In the '345 patent, the 4–week secondary dosing is one of five explicit options and the 12–week dosing is one of 14 "or more" options, yielding 70 or more combinations for the claimed initial, secondary, and tertiary dosing frequencies. In *Ruschig*, the claim at issue was directed to a single compound. 379 F.2d at 994-95. The examiner there found the specification yielded over 1,000 combinations encompassing the specific claim, but the Patent Owner argued that the total number was 46. The Federal Circuit did not find this persuasive, holding: "Specific claims to single compounds require reasonably specific supporting disclosure and while . . . naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required." *Id.* at 994. In the same way here, even if the '345 patent disclosed just 70 combinations, something more is required to reasonably support the specifics of claim 1. Such a "laundry list" disclosure ""would not 'reasonably lead' those skilled in the art to any particular" dosing frequency. *Fujikawa*, 93 F.3d at 1571; *see also FWP IP ApS v. Biogen MA, Inc.*, 749 Fed. Appx. 969, 973 (Fed. Cir. 2018) (unpublished) (finding a specific dose of 480 mg unsupported

where the specification only mentioned 480 mg three times, twice in a paragraph listing possible doses).

The '345 patent is different than those cases where the Federal Circuit found support for a claimed invention where the specification described the invention among various combinations. In those cases, the court found that one of skill in the art would recognize possession of the invention based on background knowledge in the art. Those cases cannot save the '345 patent and be consistent with Regeneron's prosecution arguments. For example, Regeneron argued during prosecution that one of skill in the art would understand a non-monthly tertiary dosing schedule to be the recognized option in the art: "At the time of the invention the standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month."[204] As evidenced by Regeneron's statement in prosecution, one of skill in the art would not look at the undifferentiated lists of dosing frequencies and recognize possession of the "non-standard" specific regimen disclosed in claim 1.

For the above reasons, the '345 patent is invalid for failing the written description requirement of 35 U.S.C. § 112(a).

[204] Ex. 1002, Response, 06/28/2019, at 7.

IX. THE BOARD SHOULD NOT EXERCISE DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(D)

Section 325(d) is inapplicable to this proceeding because the Petition does not raise substantially the same art or arguments in the same way as the examination of the '345 patent and, to the extent the Petition does, the Office erred in a material manner. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 7-11 (P.T.A.B. Feb. 13, 2020) (precedential).

A. Shams Was Not Considered on the Record, Is Not Cumulative of any Reference Considered on the Record, and, Even if It Was Considered, the Office Materially Erred by Allowing the '345 Patent over Shams

"The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharma., Inc.*, IPR2019-00740, Paper 15 at 65-66 (P.T.A.B. Aug. 30, 2019). Although Regeneron identified Shams in an Information Disclosure Statement ("IDS")[205], the Examiner did not apply Shams in an anticipation or obviousness rejection. Like the patent owner in *Amgen*, Regeneron here can only point to an IDS.

[205] Ex. 1002, IDS filed 2019-06-09.

Shams is not cumulative of any art considered during prosecution. The Office issued two principal rejections of claim 1 during prosecution—obviousness-type double patenting and anticipation by the 2009 Press Release—and Regeneron overcame the rejections by arguing that the prior art was limited to monthly dosing or the prior art did not specifically teach 12 week tertiary dosing. Crediting Regeneron's arguments, the Office withdrew both rejections because no reference taught 4 week dosing of VEGF antagonist followed by 12–week dosing; Shams teaches this purportedly novel dosing regimen. Thus, Shams 12–week dosing is not cumulative to any reference discussed on the record.

Even if the Office had considered Shams, "the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (P.T.A.B. Feb. 13, 2020) (precedential). While the Examiner may have considered Shams in an IDS, the touchstone is "the extent of such consideration" and whether there is "evidence of record indicating why the Examiner" did not reject the claims. *William Hill US Holdco, Inc. v. CG Tech. Dev.*, LLC, IPR2019-00317, Paper 14 at 35 (P.T.A.B. May 30, 2019). There is no evidence on the record that the Examiner here considered Shams substantively. "[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive." *Advanced*

Bionics at 10. Assuming the Examiner did consider Shams substantively but did not include the analysis on the record, the materiality of Shams—and the error in Office's '345 prosecution—is confirmed by prosecution in a third-party application. In U.S. Application No. 14/934,731, (the "'731 application"), Novartis filed claim 1 to cover "three individual doses of a VEGF antagonist at 4–week intervals" followed by "an additional dose of the VEGF antagonist once . . . every 12 weeks (q12 regimen) if [certain] criteria are not met."[206] The Examiner in the '731 application rejected the claimed dosing regimens as anticipated by the European national stage application (EP 2311433) of Shams' PCT, comparing the '731 application's dosing regimen to Shams' disclosure:[207]

> [Shams] teaches methods for administering a mammal suffering from, or at risk for, an intraocular neovascular disorder with regular dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist (abstract). The methods include administering to a mammal a number of first individual doses of a VEGF antagonist (ranibizumab), followed by administering to the mammal a number of second individual doses of the antibody, while the second individual doses are

[206] Ex. 1014, claims filed 11-06-2015.

[207] Ex. 1014, Non-Final Rejection mailed 11-14-2016 (citing EP 2311433).

> administered less frequently. The mammal in need of may be a human. The administration of the VEGF antagonist is intravitreal. The first individual doses are administered at one month intervals (e.g., about 3 individual doses). In another embodiment the second individual doses are administered at three month intervals (e.g., about 6 individual doses).

To the extent the Office considered Shams in the '345 patent's prosecution, the Office materially erred for not rejecting the '345 patent claims under Shams as shown by the Office's analysis of the same dosing regimen in the '731 application.

For all the foregoing reasons, the Board should decline to exercise discretion under § 325(d) for Ground 1, the '345 Patent is anticipated by Shams.

B. The 2009 Press Release in View of Shams Was Not Considered on the Record nor Were any Similar Arguments Considered

"The Board frequently holds that a reference that was neither applied against the claims nor discussed by the Examiner does not weigh in favor of exercising the Board's discretion under § 325(d) to deny a petition." *Amazon Inc. v. M2M Sols. LLC, IPR2019-01204*, Paper 14 at 17 (P.T.A.B. Jan. 23, 2020) (internal quotations omitted). As discussed above, Shams was not considered substantively on the record nor cumulative of any reference discussed on the record. Thus, the 2009 Press Release in view of Shams was not considered, and the Board should not exercise its discretion under § 325(d) to deny the present petition.

Further, the Office only considered the 2009 Press Release's 4 week plus 12 week PRN dosing regimen on the record; the press release's 4 week plus 8 week dosing regimen—relied upon in Ground 2—was never discussed. In the '345 prosecution, the third party submission only raised the 2009 Press Release's 4 week and 12 week PRN dosing[208] and only as a 102 argument; the Examiner did likewise. There is no evidence to suggest that the Office considered the 2009 Press Release's 4 week plus 8 week dosing regimen, much less consider modifying that dosing regimen to a 4 week plus 12 week dosing regimen. Thus, not only is the 2009 Press Release in view of Shams newly presented because Shams was not previously considered, but also because the 2009 Press Release was not previously considered on the record as a 103 reference nor was the 2009 Press Release's 4 week plus 8 week dosing regimen considered in a rejection.

For all the foregoing reasons, the Board should decline to exercise discretion under § 325(d) for Ground 2, the '345 Patent is obviousnes over the 2009 Press Release in view of Shams.

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[208] The third party submission introduced evidence from a second reference, Dixon, as evidence that the Press Release's "VEGF-Trap" was the claimed VEGF antagonist and, more particularly, Regeneron's aflibercept.

C. No Written Description Arguments Were Considered on the Record

The Office issued no rejections under 35 U.S.C. § 112 during prosecution of the '345 patent. Further, the Office never raised the 12 week tertiary dosing plan as lacking support. Because no 12–week dosing rejections or similar arguments were raised during prosecution, the Board should decline to deny Ground 3 under § 325(d).

X. MANDATORY NOTICES

A. Real Party-in-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), the real parties-in-interest in this proceeding are Chengdu Kanghong Biotechnology Co., Ltd. (Petitioner), Chengdu Kanghong Pharmaceutical Group Co., Ltd. (the parent company of Petitioner), and Beijing Kanghong Biomedical Co., Ltd. (a wholly-owned subsidiary of Petitioner's parent company). No other party has funded or exercises control over this Petition.

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

Petitioner is unaware of any related federal court or PTAB proceedings.

C. Lead and Back-Up Counsel and Service Information

Pursuant to 37 C.F.R. § 42.8(b)(3), Petitioner identifies the following counsel (and a power of attorney accompanies this Petition).

Lead Counsel for Petitioner	Backup Counsel for Petitioner
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Pursuant to 37 C.F.R. § 42.8(b)(4), service information for lead and back-up counsel is provided above. Petitioner consents to electronic service by email to CHENGDU-PGR@mofo.com.

XI. CONCLUSION

Because there is a reasonable likelihood that Kanghong will prevail on at least one of its asserted grounds with respect to at least one claim, Kanghong respectfully requests that the Board institute post-grant review of claims 1–11 of the '345 patent. Upon review, claims 1–11 should be held unpatentable.

The PTO is authorized to charge any required fees, including the fee as set forth in 37 C.F.R. § 42.15(a) and any excess claim fees, to Deposit Account No. **03-1952** referencing Docket No. **77688-00000.15**.

Respectfully submitted,

Dated: January 7, 2021 /Matthew I. Kreeger/

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CERTIFICATION OF WORD COUNT UNDER 37 C.F.R. § 42.24(d)

The undersigned hereby certifies that the foregoing petition contains 14,087 words according to the word count of the word-processing software used to prepare the petition, excluding the table of contents, listing of exhibits, mandatory notices under 37 C.F.R. § 42.8, certificate of service, and certificate of word count.

Dated: January 7, 2021 /Matthew I. Kreeger/

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Registration No.: 56,398

CERTIFICATE OF SERVICE (37 C.F.R. § 42.24)

I hereby certify that the attached Petition for Post Grant Review and supporting materials were served as of the below date by UPS, which is a means at least as fast and reliable as U.S. Express Mail, on the Patent Owner at the correspondence address indicated for U.S. Patent No. 10,828,345:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner

Case PGR2021-00035
Patent 10,828,345

PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.

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I. INTRODUCTION

Patent Owner Regeneron Pharmaceuticals, Inc. ("Regeneron") is an innovative U.S. biotechnology company that invents life-changing medicines for people with serious diseases. Regeneron was founded and has been led for more than 30 years by physician-scientists and has developed nine FDA-approved medicines, including EYLEA®. The active agent in EYLEA®, aflibercept, is a novel fusion protein developed by Regeneron that binds to and neutralizes Vascular Endothelial Growth Factor (VEGF), a key contributor to angiogenesis. By binding and neutralizing VEGF, aflibercept is able to prevent blood vessel leakage and block the growth of abnormal blood vessels in the back of the eye and effectively treat angiogenic eye disorders. Since its approval by FDA in 2011, EYLEA® has revolutionized the treatment of angiogenic eye disorders including age-related macular degeneration (AMD), macular edema, and diabetic retinopathy.

Before the development of EYLEA®, the standard of care for treatment of angiogenic eye disorders was monthly intravitreal injections of ranibizumab (an anti-VEGF antibody fragment) or off-label use of bevacizumab (an anti-VEGF antibody). The great treatment burden of monthly eye injections led to extensive efforts in the art to decrease injection frequency and physician monitoring. Ex. 1012 at 1, 9. However, before EYLEA, fixed quarterly or "as needed" (*pro re nata*) dosing regimens with existing VEGF inhibitors, without monthly monitoring visits, were not effective at maintaining vision. Ex. 1012 at 1.

Regeneron's Phase III clinical trial results surprisingly demonstrated "remarkably similar improvement in vision and anatomic measures can be achieved" with less frequent dosing of aflibercept as compared to monthly injections of ranibizumab. Ex. 1012 at 10-11. Indeed, the Examiner relied on this evidence of unexpected results during prosecution of U.S. Patent No. 10,828,345 (the "'345 Patent"). Not surprisingly, given the long-felt need and repeated failures in the art to reduce treatment burden and injection frequency, EYLEA has enjoyed great commercial success.

Petitioner Chengdu Kanghong Biotechnology Co., Ltd.'s ("Kanghong" or "Petitioner") seeks to capitalize on Regeneron's hard-earned success by commercializing conbercept, a "me too" fusion protein, in the United States.[1] Petitioner seeks to invalidate Regeneron's '345 Patent claims to extended (12-week) dosing regimens for treating angiogenic eye disorders using the claimed VEGF antagonist fusion proteins, by arguing that Regeneron's claims are

[1] Petitioner seeks to invalidate the '345 Patent even before the safety and efficacy of its infringing conbercept product has been demonstrated. Indeed, Petitioner recently suspended one of its two Phase III pivotal clinical trials for conbercept in the United States based on a mid-term review of data generated in the study. In addition, the National Agency for the Safety of Medicines and Health Products of France recently halted a Phase III trial of conbercept in Europe. *See* Ex. 2032; Ex. 2033; Ex. 2034.

anticipated or obvious based on a prior art dosing regimen, and are not adequately described. However, the Shams prior art dosing regimen on which Petitioner relies was an acknowledged failure and Petitioner assiduously avoids any discussion of Regeneron's demonstration of unexpected results in prosecution, on which the Examiner relied in allowing the '345 Patent. Moreover, Petitioner overlooks the fact that the dosing regimen claimed is described as a specific example in the specification.

Patent Owner submits this preliminary response pursuant to 35 U.S.C. § 323 and 37 C.F.R. § 42.207 to Petitioner's request for post-grant review ("PGR") of Claims 1-11 of the '345 Patent, Ex. 1001. This preliminary response is timely filed within three months of the Patent Trial & Appeal Board's ("Board") notice (Paper No. 3), mailed January 15, 2021, indicating that the Petition was accorded a filing date. As set forth herein and in the accompanying exhibits, the Petition should be denied for at least the following reasons:

First, the '345 Patent is not eligible for PGR because its effective filing date is before March 16, 2013.

Second, the prior art asserted by Petitioner in Grounds 1 and 2, and the §112 disclosure challenged in Ground 3, were previously before the Examiner, and Petitioner has not sufficiently alleged that the Examiner erred in a manner material to the patentability of the challenged claims in considering the art and arguments,

warranting discretionary denial under 35 U.S.C. § 325(d). *See Pharmacosmos A/S v. Am. Regent, Inc.*, PGR2020-00009, Paper 17 at 27-28 (Aug. 14, 2020).

Third, Petitioner has failed to meet its threshold burden under 35 U.S.C. §§ 324(a) and 322(a)(3) to show that it is more likely than not that at least one of the claims of the '345 Patent is unpatentable because (1) Shams does not anticipate the '345 Patent claims, (2) Shams and the 2009 Press Release do not render the '345 Patent claims obvious, and (3) the '345 Patent claims are adequately supported by the pre-March 16, 2013 priority applications.

II. BACKGROUND

A. The '345 Patent Claims

The '345 Patent's single independent claim, Claim 1, recites a method for treating an angiogenic eye disorder in a patient by administering a single dose of a VEGF antagonist followed by one or more secondary doses that are administered four weeks after the preceding dose, followed by tertiary or maintenance doses that are administered twelve weeks apart. Ex. 1001 at 21:55-22:56. Claim 1 also recites that the claimed VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGF receptor Flt1, Ig domain 3 of the VEGF receptor Flk1, and a multimerizing component. *Id.* In other words, Claim 1 recites a method of treating an angiogenic eye disorder by administering a recited

VEGF antagonist fusion protein at a twelve-week dosing regimen following an initial set of doses administered four weeks apart. *Id.*

The '345 Patent has ten dependent claims, Claims 2-11. Claim 2 recites that the particular VEGF antagonist fusion protein is aflibercept, the fusion protein in Regeneron's Eylea® product. *Id.* at 22:56-57. Claims 3 and 4 recite that the VEGF antagonist fusion protein is administered intraocularly and intravitreally, respectively. *Id.* at 22:58-62. Claim 5 recites administering 0.5 to 2 mg, Claim 6 recites administering 0.5 mg, and Claim 7 recites administering 2 mg of VEGF antagonist. *Id.* at 22:63-23:2. Claim 8 recites that the angiogenic eye disorder is one of: age related macular degeneration (also known as "wet AMD"), diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization; Claim 9 recites that the angiogenic eye disorder is wet AMD; Claim 10 recites that the angiogenic eye disorder is diabetic retinopathy and Claim 11 recites that the angiogenic eye is diabetic macular edema. *Id.*

III. THE LEVEL OF ORDINARY SKILL IN THE ART

For purposes of this Preliminary Response, Patent Owner has used Petitioner's definition of the person of ordinary skill in the art ("POSA"). Paper 2 at 16. Patent Owner reserves the right to propose another definition if this post-grant review is instituted.

IV. CLAIM CONSTRUCTION

The claims in a post-grant review are to be construed using the same standard that applies in district court proceedings, which is set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Circ. 2005) (*en banc*); *see Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board*, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (applicable to post-grant reviews filed on or after November 13, 2018).

Petitioner's challenge should be disposed of under 35 U.S.C. § 325. However, should the Board consider it necessary to decide whether Petitioner satisfied its threshold burden under 35 U.S.C. § 324, the proposed claim constructions are relevant to Petitioner's Ground 1 and 2 challenges.[2] As explained below, Patent Owner respectfully submits that "A method for treating an angiogenic eye disorder in a patient" is a positive limitation of Claim 1 that requires a therapeutically effective method for treating an angiogenic eye disorder and that the term "tertiary dose" means "dose(s) that maintain(s) a therapeutic

[2] Petitioner did not propose any constructions and, indeed, argued that no construction is required for any of the terms used in the '345 Patent. Paper 2 at 16-17.

effect throughout the course of treatment."[3]

A. Claim 1's Preamble Is a Positive Limitation That Requires A Therapeutically Effective Method of Treatment

The preamble of Claim 1 — "A method of treating an angiogenic eye disorder in a patient" — is limiting because it breathes life and meaning into the claim. Further, it provides an antecedent basis for terms in the body of the claim and dependent claims.

The preamble of Claim 1 gives the claim life and meaning. *See, e.g.*, *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002); *see also Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003); *Novartis Pharms. Corp. v. Accord Healthcare Inc.*, 387 F. Supp. 3d 429, 436 (D. Del. 2019). It sets forth the essence of the claimed invention — "treat[ment] of an angiogenic eye disorder in a patient." Ex. 1001 at Claim 1; *see also* Ex. 1001 at Abstract ("The present invention provides methods for treating angiogenic eye disorders …."); *id.* at 2:3-18 (same); *Griffin*, 285 F.3d at 1033 (construing preamble that recites a "method for diagnosing" as limiting because "[d]iagnosis is … the essence of th[e] invention; its appearance in the count gives 'life and meaning' to the manipulative steps").

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[3] Patent Owner reserves the right to propose additional or different constructions for claim terms in this proceeding in response to a Decision on Institution or any arguments raised by Petitioner in any future submission.

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

The Claim 1 preamble (which recites "a patient" and "an angiogenic eye disorder") provides an antecedent basis for "the patient" who is treated and for the "angiogenic eye disorders" that are specified in dependent Claims 8-11. The method comprises "sequentially administering ***to the patient***" doses of VEGF antagonist. Ex. 1001 at Claim 1 (emphasis added). This "sequentially administering" step depends upon the preamble. Without the preamble, it would be unclear ***who*** is receiving sequentially administered doses. Likewise, dependent Claims 8-11 rely on the preamble for their antecedent basis because they recite the particular "angiogenic eye disorder[s]" to be treated. *See id.* at Claims 8-11.

Because the preamble of Claim 1 provides an antecedent basis on which other claim limitations rely, it is a positive limitation of the claim. *See, e.g.*, *Sanofi Mature IP v. Mylan Labs. Ltd.*, 757 F. App'x 988, 993 (Fed. Cir. 2019) (finding the preamble — "a method of increasing survival" — to be limiting because it provides an antecedent basis for which a later limitation — "a patient in need thereof" — relied); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed Cir. 2001); *GlaxoSmithKline LLC v. Glenmark Pharms. Inc. USA*, No. 14-877-LPS-CJB, Dkt. 133 at 14-15 (D. Del. June 3, 2016) *adopted*, 2017 WL 658468 (construing preamble — "decreasing mortality caused by congestive heart failure in a patient in need thereof" — to be limiting because term in claim body — "said patient" — "relies on and derives antecedent basis" therefrom).

Thus, the preamble of Claim 1, "A method for treating an angiogenic eye disorder in a patient" is limiting because it breathes life and meaning into the claim and provides an antecedent basis for other limitations in the body of Claim 1 and the dependent claims, thus requiring a therapeutically effective method for treating an angiogenic eye disorder.

B. The "Tertiary Dose" Must Maintain the Therapeutic Effect During Treatment

Patent Owner respectfully submits that the claim term "tertiary dose" means "dose(s) that maintain(s) a therapeutic effect throughout the course of treatment."

Under the *Phillips* standard, claim terms are afforded "their ordinary and customary meaning," which is "the meaning that the term would have to a person

of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1312-13. But where a term has "no previous meaning to those of ordinary skill in the prior art," one looks "[elsewhere] in the patent." *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004); *see also MyMail, Ltd. v. Am. Online, Inc.*, 476 F.3d 1372, 1376 (Fed. Cir. 2007) (construing "coined term" that was "without a meaning apart from the patent" in view of the specification). The specification is highly relevant and often dispositive to the claim construction analysis; it is "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

The plain language of Claim 1 conveys that one or more "tertiary doses" are to be administered 12 weeks after the preceding dose. However, the term "tertiary dose" does not have a "previous meaning to those of ordinary skill in the art," (Ex. 2001 ¶ 21), "apart from the patent." *Irdeto Access, Inc.*, 383 F.3d at 1300; *MyMail, Ltd.*, 476 F.3d at 1376. Accordingly, the Board must look to the '345 Patent specification to construe the term. *Irdeto Access, Inc.*, 383 F.3d at 1300; *MyMail, Ltd.*, 476 F.3d at 1376.

The '345 Patent specification explains that, at the time of patent filing in January 2011, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001 at 1:57-63. Nonetheless, the '345 Patent recognized that there remained a need for less frequent dosing regimens that could

maintain a high degree of efficacy. *Id.* at 1: 64-67. The '345 Patent successfully addressed this long-felt need:

> The present inventors have ***surprisingly*** discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.

Id. at 2:3-18 (emphases added). Indeed, the '345 Patent discloses that a key benefit of the claimed dosing regimens is that for "most of the course of treatment (*i.e.* the ***tertiary doses***)," *id.* at 2:24-31 (emphasis added), patients may be treated less frequently as compared to therapies that existed in the art. Simply put, the disclosed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy. Accordingly, read in view of the specification, the term "tertiary dose" means "dose(s) that maintain(s) a therapeutic effect throughout the course of treatment."

V. THE '345 PATENT IS NOT ELIGIBLE FOR POST-GRANT REVIEW

The '345 Patent claims priority to three provisional applications filed in January of 2011 through a series of continuation applications and one continuation-

in-part application.[4] Petitioner offers two arguments in support of its assertion that the '345 Patent is eligible for PGR. Paper 2 at 5, 23. First, Petitioner argues that dependent Claim 8, which is directed to treatment of BRVO, is supported only by a continuation-in-part ("CIP") application filed July 12, 2013. Second, Petitioner argues that the quarterly (12-week) dosing regimen recited in each of the challenged claims lacks adequate written description support. However, for the reasons discussed below, all of challenged claims are supported by the pre-AIA 2011 Provisional Applications and, therefore, the '345 Patent is not eligible for PGR.

A. The Examiner Already Determined That the '345 Patent Should Be Reviewed Under Pre-AIA Standards

During prosecution, the Examiner explicitly examined the '282 application, which issued as the '345 Patent, under pre-AIA patentability standards. On each Office Action Summary sheet, the examiner noted "No" in the AIA (FITF) Status box, and began the remarks by stating that the "present application is being examined under the pre-AIA first to invent provisions." *See* Ex. 1002 at 113-14, 143-44, 224-

[4] Provisional Application 61/432,245 was filed on January 13, 2011 (Ex. 1045) ("the '245 Application"), provisional application 61/434,836 was filed on January 21, 2011 (Ex. 1046) ("the '836 Application"), and provisional application 61/561,957 was filed on November 21, 2011 (Ex. 1047) ("the '957 Application") (collectively, the provisional applications are the "2011 Provisional Applications").

25, 322-23. The examiner issued and analyzed rejections under "pre-AIA 35 U.S.C. 102(b)." *Id.* at 144-45, 227. The "effective filing date" for the purposes of patent prosecution and PTAB proceedings rely on the same statutory definition, thus the priority analysis is identical. *See* AIA § 3(n)(1).

The Board has previously declined to find a patent PGR-eligible where an Examiner explicitly examined the challenged patents under the pre-AIA first-to-invent provisions. *See Mylan Pharms. Inc. v. Yeda Research & Dev. Co. Ltd.*, PGR2016-00010, Paper 9 at 6-10 (Aug. 15, 2016) (finding patent was not PGR eligible based in part on "the Examiner's findings as to the effective filing date of the [challenged patent] during prosecution."); *see also Merck Sharp & Dohme Corp. v. Wyeth LLC*, PGR2017-00016 & PGR2017-00017, Paper 9 (Oct. 20, 2017) (relying on the Examiner's marking of "No" in the AIA status box in making the determination that the patent was not eligible for post-grant review). Although the Board has said that it does not treat these designations made during prosecution as entirely dispositive of the issue of PGR eligibility, it has reaffirmed the relevance of these designations in deciding eligibility. *See e.g., Commonwealth Sci. & Indus. Research v. BASF Plant Sci. GMBH*, PGR2020-0003, Paper 11 (Sept. 10, 2020).

During prosecution, Regeneron relied upon the Examiner's pre-AIA finding in formulating its arguments for patentability, and should be entitled to rely on that

determination now. For this reason alone, the Board should decline to find that the '345 is eligible for post-grant review.

B. The 2011 Provisional Applications Describe Treatment of Branch Retinal Vein Occlusion (BRVO)

1. Because the 2011 Provisional Applications Support the Challenged Claims, the '345 Patent Is Not PGR Eligible

Petitioner ignores the support provided in the 2011 Provisional Applications for treatment of all angiogenic eye disorders, which a skilled artisan would have known included BRVO. It also ignores that BRVO was known to be treatable with certain VEGF antagonists and that, based on the 2011 Provisional Applications' disclosure of demonstrated efficacy in wAMD, DME, and CRVO, a skilled artisan would understand the '345 Patent inventors to be in possession of a method of treating BRVO with a VEGF antagonist fusion protein as claimed.

Instead of contending with this support and the knowledge of the skilled artisan at the time, Petitioner simply asserts that because Claim 8 specifically recites treating "BRVO," the claim was not supported until the term "BRVO" was added to the specification by continuation-in-part application No. 13/940,370 (the '370 Application), filed on July 12, 2013. Paper 2 at 18. Claim 8, however, need not rely upon the post-AIA '370 Application for support because the priority applications'

disclosure of treating angiogenic eye disorders in general and central retinal vein occlusion ("CRVO") in particular adequately supports Claim 8.[5]

Under the AIA, if an application is filed after March 16, 2013 and claims the benefit of an application filed before March 16, 2013, the application is considered to be a "transition application" for purposes of the AIA. *See* MPEP § 210; AIA § 3(n)(1). Whether the AIA applies to a transition application is determined by the claims' effective filing date, as defined by 35 U.S.C. § 100(i)(1); *Merck Sharp & Dohme*, PGR2017-00016 & PGR2017-00017, Paper 9 at 6-7. The "effective filing date" in this context is the filing date of the earliest application for which the patent or application is entitled, as to such invention, to a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c)." 35 U.S.C. § 100(i)(1)(B). The fact that descriptive matter is added in a CIP application does not presumptively determine priority for the contents of the application; rather, priority is determined on a claim-by-claim basis and depends on compliance with 35 U.S.C. §§ 120 and

[5] *See* No. 61/432,245 (Ex. 1045) filed on January 13, 2011 and No. 61/561,957 (Ex. 1047) filed on November 21, 2011.

112(a).[6] Because the CIP subject matter is not relied upon by any of the challenged claims for § 112 support, *see infra* pp. 19-24, all claims of the '345 Patent have an effective filing date that pre-dates the AIA. Congress did not intend such patents to be subject to PGR, and instead explicitly provided for alternative mechanisms, such as *inter partes* review, for invalidity challenges to these pre-AIA patents.

2. Treatment of Branch Retinal Vein Occlusion (BRVO) Was Described by the 2011 Provisional Applications

a. By January 2011, A POSA Would Have Understood BRVO to Be Within the Patent's Disclosure of "Angiogenic Eye Disorders"

The stated purpose of the first provisional application, filed January 13, 2011, is to "treat any angiogenic eye disorder," explaining that an angiogenic eye disorder means "***any*** disease of the eye which is caused by or associated with the growth or

[6] *See* MPEP § 211.05 I.B. ("claims of the continuation-in-part application that are disclosed in the manner provided by 35 U.S.C. 112(a) in the prior-filed application are entitled to the benefit of the filing date of the prior filed application"); *see also Therma-Tru Corp. v. Peachtree Doors Inc.*, 44 F.3d 988, 992 (Fed. Cir. 1995) ("A claim in a CIP application is entitled to the filing date of the parent application when the claimed invention is described in the parent specification in a manner that satisfies, inter alia, the description requirement of 35 U.S.C. § 112.") (citing *Kennecott Corp. v. Kyocera Int'l Inc.*, 835 F.2d 1419, 1421 (Fed. Cir. 1987)).

proliferation of blood vessels or by blood vessel leakage." Ex. 1045 at [0024] (emphasis added); *see also* [0031] ("The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder.").

Petitioner ignores the fact that a POSA in 2011 would have known that "angiogenic eye disorders" was a well-defined class of diseases that included branch retinal vein occlusion ("BRVO"). Ex. 2001 ¶¶ 26-28; *see also* Ex. 2003 at 2 (a 2009 listing of "angiogenic eye disorders," including "branch RVO"). Likewise, by 2011, a POSA would have known that angiogenic eye disorders may be treated by VEGF antagonists. Ex. 2001 ¶ 29; Ex. 1001 at 1:54-56 ("[I]nhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders"). The etiology of angiogenic eye disorders and the rationale for VEGF therapy had been widely-recognized before 2011. Ex. 2001 ¶¶ 26-27, 35, 38; Ex. 2004 at 23.

Additionally, by the earliest 2011 priority filing date, a POSA would have known that certain VEGF antagonists had proven effective, and were even FDA-approved, for the treatment of BRVO. Ex. 2001 ¶¶ 38-43. Accordingly, when the priority applications taught that the claimed VEGF antagonists could be used to treat angiogenic eye disorders, a POSA would have understood and immediately recognized that "angiogenic eye disorders" specifically included BRVO as a known

angiogenic eye disorder that was treatable using a VEGF antagonist. Ex. 2001 ¶¶ 44-46.

Petitioner contends that the skilled artisan "would not understand that successful treatment of one vascular disease … means another (*e.g.*, BRVO) is ***necessarily*** treated." Paper 2 at 21 (emphasis added). This argument ignores the priority applications' teaching that the claimed method could be used for ***any*** angiogenic eye disorder. Ex. 1001 at 1:54-56. It also ignores the fact that BRVO had already been shown to be successfully treated by anti-VEGF agents before 2011. Ex. 2001 ¶¶ 39-43.

Based on the known etiology of BRVO by 2011 and the specific demonstration in the art that anti-VEGF agents had successfully treated BRVO, a POSA would have understood that BRVO was "an angiogenic eye disorder" "which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage," and understood the 2011 Provisional Applications to disclose methods of treating BRVO.

b. The 2011 Provisional Applications' Disclosure of CRVO Treatment Would Have Provided a POSA With Confirmation That BRVO Was Among the Angiogenic Eye Disorders That Could Be Treated By the Claimed Dosing Regimens

Not only would a POSA have understood from the general disclosure that BRVO is an "angiogenic eye disorder" that could be treated with the claimed anti-

VEGF fusion proteins, but the '245 Application specifically describes treatment of CRVO as one type of angiogenic eye disorder and thus confirms that the disclosed treatment methods include treatment of BRVO. Ex. 1045 at [0024] ("Non-limiting examples of angiogenic eye disorders that are treatable using the method of the present invention include … central retinal vein occlusion"). CRVO, like BRVO, is a type of retinal vein occlusion. Retinal vein occlusions result from the development of thrombus in the retinal vein resulting in reduced blood flow and exhibit other similar pathologies, including VEGF up-regulation. Ex. 2001 ¶ 37. The principle distinction between the two diseases is the locus of the occlusion in the retinal veins, but in both cases the occlusion occurs from VEGF up-regulation and is treatable with an anti-VEGF agent. Ex. 2001 ¶ 37. By 2011, a POSA would have recognized a disclosure of treatment of CRVO with an anti-VEGF agent as an indicator for successful treatment of BRVO with the same type of therapy.

Petitioner argues that a POSA would not have recognized that a CRVO treatment would be used for BRVO because the diseases have anatomic differences, affect different patient populations and, historically, had different standards of care. Paper 2 at 22; Ex. 1003 ¶¶ 126-127. None of those differences were relevant by 2011 because, by that time, the skilled artisan understood that the two diseases shared a common etiology rooted in VEGF upregulation and, further, that both could be treated successfully with anti-VEGF therapies. Indeed, by 2011, clinical trials

showed successful treatment of CRVO and BRVO by anti-VEGF antagonists ranibizumab (Lucentis) and bevacizumab (Avastin). Ex. 2001 ¶ ¶ 39-42.[7] In fact, clinicians had successfully treated patients with both types of retinal vein occlusions with off-label Avastin since approximately 2006, and by June 2010, Lucentis had received FDA approval for treatment of both indications. Ex. 2001 ¶¶ 43, 48; Ex. 2005. Further, the retina community frequently described these developments in the treatment of BRVO and CRVO in tandem. Ex. 2001 ¶ 51; Ex. 2006 at 2 (discussing Lucentis phase III BRVO and CRVO trials together).

[7] As with all other evidentiary questions at the institution stage, the burden is on Petitioner to show that it is more likely than not that at least one challenged claim is unpatentable. *See* 35 U.S.C. § 324(a); *see also Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29, at 16-20 (Dec. 20, 2019). Consistent with this statutory framework and Petitioner's ultimate burden of proof, the Board should consider all evidence and apply no evidentiary presumption for testimonial evidence favoring Petitioner. *See also* 85 Fed. Reg. 79120 (Dec. 9, 2020) (consistent with this statutory framework, USPTO has revised its rules to ensure any testimonial evidence submitted with a POPR will be taken into account in the totality of the evidence).

In addition to the success of other anti-VEGF agents, Regeneron's own anti-VEGF therapy had demonstrated efficacy in treating CRVO and was disclosed in the '957 Application, filed on November 21, 2011. The '957 Application disclosed the 24 and 52 week results of Regeneron's Phase III trial in CRVO, which demonstrated statistically significant improvements in visual acuity as compared to sham control. Ex. 2001 ¶ 55; Ex. 1047 at [0064]-[0066].

Accordingly, the knowledge of the skilled artisan combined with the disclosures in the '345 Patent's earliest provisional applications adequately support Claim 8.

C. The Claimed Twelve-Week Dosing Regimen Is Fully Supported by the 2011 Provisional Applications

For the reasons discussed below, *infra* Section VII.C, the 12-week dosing regimen recited in the '345 Patent claims is supported by the 2011 Provisional Applications. Because both written description challenges fail to establish PGR eligibility, the Petition should be denied.

VI. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(d)

The Board should exercise its discretion and deny institution under 35 U.S.C. § 325(d) because Petitioner relies on the same art and arguments that were considered by the Examiner during prosecution of the '345 Patent and fails to show

that, in considering that art, the Examiner made any error material to the patentability of the challenged claims.

The Board applies a two-part framework to analyze discretionary denial under § 325(d): "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (Feb. 13, 2020) (precedential), citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

Petitioner misstates this standard and incorrectly suggests that the art and arguments must have been raised ***in the same way*** as it was during prosecution for §325(d) to apply. Paper 2 at 71. That is not correct. Rather, the Board has held that §325(d) discretionary denial is appropriate where the same or substantially the same art or argument was previously presented to the Office, regardless of how it was applied or considered by the Examiner. *Advanced Bionics*, 2020 WL 740292, at *3. If the art or argument were previously presented, the Board moves on to determine if Petitioner has shown that the Office materially erred. *Id.*

A. The Examiner Considered the Same or Substantially the Same Art and Arguments During Prosecution (*Becton, Dickinson* factors (a), (b), and (d)[8])

Petitioner's Grounds rely upon the same art and arguments that were presented to, and considered by, the Examiner during prosecution of the '345 Patent, thus satisfying step one of the *Advanced Bionics* framework. In Ground 1, Petitioner argues that the '345 Patent claims are anticipated by Shams (Ex. 1004); in Ground 2, Petitioner argues that the '345 Patent claims are rendered obvious by the 2009 Press Release (Ex. 1005) in view of Shams; and in Ground 3, Petitioner argues that the '345 Patent claims lack adequate written description.

1. Shams (Ex. 1004)

Shams WO 2006/047325 (Ex. 1004) is an abandoned Genentech, Inc. ("Genentech") patent application, which published on May 4, 2006 from PCT/US2005/038006. Regeneron presented Shams to the Office in an Information

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[8] *Becton, Dickinson* factors: (a) similarities and material differences between the asserted art and prior art involved during examination; (b) cumulative nature of the asserted art and prior art evaluated during examination; and (d) extent of overlap between arguments made during examination and the manner in which petitioner relies on the prior art. *See Becton, Dickinson*, IPR2017-01586, Paper 8 at 17–18 (precedential as to § III.C.5, first paragraph).

Disclosure Statement ("IDS") that was considered by the Examiner during prosecution of the '345 Patent. Ex. 1002 at 225, 239. Shams is cited on the face of the '345 Patent. Ex. 1001 at 1. Petitioner admits that Shams was submitted in an IDS and marked "considered" by the Examiner during prosecution.[9] Paper 2 at 71.

Citing a single pre-*Advanced Bionics* decision, Petitioner argues that "[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." Paper 2 at 71. However, the Board has expressly rejected this argument, stating that *Advanced Bionics* provides that "previously presented art includes art made of record … such as on an [IDS]." *See, e.g.*, *Biocon Pharma Ltd. v. Novartis Pharms. Corp.*, IPR2020-01263, 2021 WL 608300, at *4 (Feb. 16, 2021) (citing *Advanced Bionics*, 2020 WL 740292, at *3); *see also Philip Morris Prods., S.A. v. Rai Strategic Holdings, Inc.*, IPR2020-00921, 2020 WL 6750120, at *5 (Nov. 16, 2020) ("the art presented in the Petition is the same as the art previously presented to the Office during examination because all of Petitioner's

[9] Ex. 1002 at 225 ("The information disclosure statement (IDS) submitted on 19 June 2019 … [has] been considered by the Examiner."); *id.* at 239 ("ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH") (Shams not lined through).

references were cited in an IDS and are listed as cited art on the front face of the '268 Patent."); *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, 2020 WL 2478503, at *6 (May 12, 2020) ("Petitioner's emphasis on the absence of any prior art rejection as if dispositive on the 325(d) inquiry is, thus, misplaced; the first part of the § 325(d) framework may be met when relied-upon art is presented in an IDS but never discussed or cited in a rejection by the Examiner..."). Thus, Shams was previously presented to and considered by the Office.

2. 2009 Press Release (Ex. 1005)

The 2009 Press Release is entitled, "Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)," and labeled with a date of September 14, 2009. The 2009 Press Release appears on the face of the '345 Patent. Ex. 1001 at 8. Petitioner admits that the 2009 Press Release was the basis for a rejection under 35 U.S.C. § 102 during the prosecution of the '345 Patent, which was overcome by Regeneron. Paper 2 at 2, 75.

Since *Advanced Bionics*, the Board has consistently found that a reference was previously provided to the Office when it is part of the basis of a rejection during prosecution. *E.g.*, *Balt USA, LLC v. Microvention, Inc.*, IPR2020-01259, 2021 WL 219251, at *8 (Jan. 21, 2021); *Gofire, Inc. v. Canopy Growth Corp.*, IPR2020-00044, 2020 WL 5991725, at *4 (Oct. 9, 2020); *Flex Logix Techs., Inc. v. Konda*, IPR2020-

00262, 2020 WL 4462127, at *4 (Aug. 3, 2020); *GlaxoSmithKline Consumer Healthcare Holdings (US) LLC v. Cipla Ltd.*, IPR2020-00371, 2020 WL 4390665, at *6 (July 31, 2020); *Samsung Elec. Co., Ltd. v. Neodron Ltd.*, IPR2020-00334, 2020 WL 3892132, at *5 (Jul. 10, 2020); *Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, 2020 WL 2206972, at *6 (May 5, 2020). Thus, the 2009 Press Release was previously presented to and considered by the Office.

3. Written Description

Petitioner asserts that the Board should decline to exercise its discretion under § 325(d) with respect to Ground 3 (written description) because "no 12-week dosing regimen rejections or similar rejections were raised during prosecution." Paper 2 at 76. Following *Advanced Bionics* and its progeny, the Board is entitled to find that the same or substantially the same arguments or issues were presented to the Examiner during prosecution even in the absence of an express rejection. *See Universal Imaging Indus., LLC v. Lexmark Int'l Inc.*, IPR2019-01387, 2020 WL

2201770, at *3-4 (May 4, 2020).[10] Moreover, the prosecution history reveals that the Examiner reviewed the specification of the '345 Patent and considered written description support in the instant application and related applications in the priority

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[10] The Board has not addressed whether, post-*Advanced Bionics*, an Examiner is presumed to have considered the adequacy of written description support for claims during prosecution. However, such a presumption is consistent with the burden-shifting framework of *Advanced Bionics*. As *Advanced Bionics* explains, "[a]t bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." 2020 WL 740292, at *3. While the Board in *Hybridgenics v. Forma Therapeutics* found that the absence of a written description rejection did not establish that an Examiner had considered written description arguments, that decision is inapplicable here. *See* PGR2018-00098, Paper 10 at 20-21 (Mar. 20, 2019). Not only is *Hybrigenics* a non-precedential pre-*Advanced Bionics* decision, but the concern that animated the Board's decision in *Hybrigenics* — that "[t]o find otherwise would potentially suggest that we should apply our discretion under 325(d) to deny review in every post-grant review where written description is challenged…" (*Id.* at 20) — ignores the fact that *Advanced Bionics* creates a rebuttable presumption that a Petitioner can overcome by showing material error.

chain. In light of Patent Owner's evidence that the Examiner considered the specification, Petitioner should be required to show error material to patentability. Petitioner fails to even so allege.

Petitioner relies only on the absence of a written description rejection as evidence that the Examiner did not consider §112. However, consistent with *Advanced Bionics*, the Examiner should be presumed to have reviewed and understood the '345 Patent's disclosures relating to the claimed 12-week dosing regimen. The Board has noted "[i]t is reasonable to assume that the Examiner read the Specification and understood these statements as part of examining" the '345 Patent. *Universal Imaging Indus., LLC v. Lexmark Int'l, Inc.*, IPR2019-01387, 2020 WL 959375, at *6 (Feb. 27, 2020). Likewise, there is a presumption that an adequate written description of the claimed invention is present in the specification as filed. MPEP § 2163. By analogy, in the context of *inter partes* review, the Board has held that an Examiner is presumed to be aware of the substantive disclosure of the material incorporated by reference into and which effectively becomes part of the specification. *Free Stream Media Corp. v. Alphonso Inc.*, IPR2019-00762, 2019 WL 4200650, at *5 (Sept. 4, 2019) (citing *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001); *see Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC*, IPR2020-01348, 2021 WL 838428, at *5 (Mar. 4, 2021).

Furthermore, the prosecution history of the '345 Patent shows that the Examiner did consider the adequacy of the specification's disclosure. In particular, Patent Owner submitted the now-issued '345 Patent claims by way of a preliminary amendment, adding new claims that included the 12-week dosing regimen. Ex. 1002 at 386. In the arguments/remarks presented to the Examiner, Patent Owner asserted that support for the new 12-week dosing claims could be found in the originally-pending claims and in the specification. Ex. 1002 at 389. Pursuant to §1.121(f), no amendment may introduce new matter into the disclosure of an application. 37 CFR §1.121(f); *see Kolmes v. World Fibers Corp.*, 107 F.3d 1534, 1538-39 (Fed. Cir. 1997). Additionally, an examiner is obligated to review the specification and determine whether the invention as claimed complies with all statutory requirements, including §112. MPEP § 2103 ("Examiners will review the complete specification."). In a Non-Final Rejection dated April 3, 2019, the Examiner confirmed that the preliminary amendment had been entered in full, *i.e.*, the Examiner found adequate support in the specification for the newly-filed claims that included the 12-week dosing regimen. Ex. 1002 at 323. Thus, the issue of the §112 sufficiency of the 12-week dosing claims was previously considered by the Examiner, as reflected by the Examiner's entry of the preliminary amendment.

In addition, the prosecution history of related family members of the '345 Patent confirms that the Examiner reviewed and considered the disclosure of the

'345 specification. In several applications leading to the '345 Patent, including the '282 Application, after entering the preliminary amendment, the Examiner objected to the specification because it did not include "[a]n updated status of the parent nonprovisional application" as "the first sentence." Ex. 1002 at 323. Regeneron amended the specification to address the Examiner's objection. Ex. 1002 at 278. In light of the amendment, the Examiner withdrew his objection. Ex. 1002 at 225. In several other applications in the priority chain, the Examiner made informality-based objections to the specification's disclosure that Regeneron similarly overcame. *E.g.*, Ex. 2007 at 151 (objecting to specification because "[a]n updated status of the parent nonprovisional application should be included in the first sentence"); Ex. 2008at 104 (same). And, in S.N. 13/940,370, another application in the priority chain that issued as U.S. Patent No. 9,254,338, the Examiner rejected pending claims for lack of written description. Ex. 2009 at 262-264. Accordingly, the prosecution history reflects that the Examiner considered the specifications as well as potential § 112 issues in reviewing Regeneron's dosing regimen applications.

B. Petitioner Fails to Show That the Examiner Erred in a Manner Material to Patentability (*Becton, Dickinson* factors (c), (e), and (f)[11])

As step one has been satisfied, Petitioner must show that the Office erred in a manner material to the patentability of the challenged claims. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Advanced Bionics*, 2020 WL 740292, at *4 n.9. "If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.* at *4.

1. Petitioner Fails to Show That the Examiner Erred in a Manner Material to Patentability in His Analysis of Shams (Ground 1)

Petitioner does not identify any "material error" that the Examiner committed ***in this case***. Petitioner cannot demonstrate material error simply because Shams

[11] *Becton, Dickinson* factors: (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments. *See Becton, Dickinson*, IPR2017-01586, Paper 8 at 17-18.

was not substantively discussed in the prosecution record. *Universal Imaging*, 2020 WL 959375, at *5 (finding that the absence of a rejection based upon the petitioned grounds "is not the end of [the Board's] analysis" on material error). Instead, the Board considers the Examiner's familiarity with the substance of the petitioned reference. *Id.* As shown above, the prosecution record indicates that the Examiner was familiar with Shams. *Supra* Section VI.A.1; *see Husky Injection Molding Sys., Ltd. v. Plastipak Packaging, Inc.*, IPR2020-00438, 2020 WL 4353621, at *7 (July 29, 2020) (in determining petitioner did not meet its burden under step two, finding statement that "all references considered except where lined through" in prosecution record indicated that the Examiner substantively considered asserted reference).

Petitioner points to the prosecution of an entirely unrelated patent application, involving a different therapeutic agent, specification and claims, where a different examiner applied Shams' alleged disclosure of a 12-week dosing regimen to reject the claims as-filed.[12] Paper 2 at 73-74. But, the Petition is silent as to what error the Examiner purportedly committed during the prosecution of the '345 Patent. At best, this extrinsic evidence indicates that "reasonable minds disagree[d] regarding the

[12] Notably, Novartis overcame the rejection based on the European equivalent of Shams, and a patent issued with claims reciting the 12-week dosing element. *E.g.*, U.S. Patent No. 10,035,850 at 17:43-18:43.

purported treatment of the art or arguments," which is insufficient to show "that the Office erred in a manner material to patentability." *Advanced Bionics*, 2020 WL 740292, at *3;[13] *see also Regeneron Pharms., Inc. v. Kymab Ltd.*, IPR2020-00389, 2020 WL 2738613, at *7 (May 26, 2020) (petitioner only offered "a different interpretation" of prior art, which is not material error). The mere fact that one examiner applied Shams in a rejection, while another marked it as cited and considered, is not enough for Petitioner to meet its burden to show that the Examiner committed material error. *Sony Interactive Entm't LLC v. Terminal Realty, Inc.*, IPR2020-00711, 2020 WL 6065188, at *5 (Oct. 13, 2020) (finding that Petitioner's argument that the asserted references were not evaluated by the examiner failed to

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[13] Petitioner's reliance on *Advanced Bionics* is inapposite. Paper 2 at 72-73. There, the claims at issue were rejected in view of the petitioned reference during prosecution. 2020 WL 740292 at *8. In dicta, the Board postulated that a petitioner may be able to show error if the record is silent or not well developed with respect to a reference. *Id.* at *4. But a silent record is not dispositive; Petitioner is still required to identify Examiner error. *Id.* at *3 ("At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record ***unless material error is shown***.") (emphasis added). Likewise, a disagreement with the Examiner is not material error. *Id.*

sufficiently identify Examiner error). In *Sony Interactive*, the Board noted that "Sony [Petitioner] was provided the opportunity to provide explanation [of material error], but Sony was silent in this regard.... Accordingly, *Becton, Dickinson* Factor (e) favors exercising our discretion to deny institution." *Id.* Similarly, here Petitioner fails to identify any material error that the Examiner purportedly committed in his consideration of Shams.

2. Petitioner Does Not Argue That the Examiner Erred in a Manner Material to Patentability as to the 2009 Press Release or Written Description (Grounds 2 and 3)

Petitioner does not allege that the Examiner committed any error during prosecution with respect to its analysis of the 2009 Press Release or the written description requirement. In fact, Petitioner is entirely silent in that regard.

The Board has found a petitioner's failure to allege material error to be a sufficient basis to determine that petitioner did not carry its burden to meet step two. *E.g.*, *Balt*, 2021 WL 219251, at *10 (Petitioner's own independent analysis of prior art without reference to or discussion of Examiner's analysis is insufficient to show material error); *NXP USA, Inc. v. Impinj, Inc.*, IPR2020-00519, 2020 WL 4805424, at *5 (Aug. 17, 2020) (no discussion of material error); *GlaxoSmithKline Consumer Healthcare Holdings (US) LLC v. Cipla Ltd.*, IPR2020-00369, 2020 WL 4390663, at *5 (July 31, 2020) (step two not met when, in part, petitioner did not "explicitly allege error in the Examiner's previous consideration of the prior art or arguments").

Petitioner asserts only that the combination of the 2009 Press Release in view of Shams was not considered during prosecution, and that the 2009 Press Release was not considered for a portion of its disclosure (8-week dosing) or as a §103 reference. Paper 2 at 75. Petitioner is splitting hairs. Petitioner does not dispute that the substance of the 2009 Press Release was expressly considered by the Examiner as the basis for a §102(b) rejection. Ex. 1002 at 227-228. Moreover, the 2009 Press Release is two pages long. Ex. 1005 at 1-2. The disclosure of the 8-week dosing regimen appears in the same paragraph as the PRN regimen capped at 12 weeks. Ex. 1002 at 1. In light of this, it is not credible for Petitioner to allege that the Examiner was not aware of or did not consider the 2009 Press Release, including its disclosure of 8-week dosing. Paper 2 at 75.

Additionally, Petitioner does not substantively address the evidence of unexpected results presented during the prosecution of the '345 Patent. In response to a double patenting rejection, Regeneron argued that even if the claimed invention were *prima facie* obvious, that finding would be overcome by the fact that the

claimed invention exhibits unexpected results.[14] Ex. 1002 at 284-286. The Examiner withdrew his rejection, in pertinent part because of Regeneron's "persuasive arguments as they pertain to the rejection…." Ex. 1002 at 225-226. Noticeably absent from the Petition is any argument that the Examiner committed material error when he found this evidence persuasive. The Board has found that petitioner did not meet its burden under step two when it failed to show that the examiner's reliance on the unexpected results was material error. *Biocon Pharma*, 2021 WL 608300, at *6-7; *see also Apotex Inc. v. Celgene Corp.*, IPR2018-00685, 2020 WL 2095846, at *4-5 (Apr. 30. 2020) (step two not met when petitioner did not advance "any argument or evidence that the Examiner erred in evaluating or

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[14] During prosecution, Regeneron argued that monthly administrations of ranibizumab were "(1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment visit," and thus there was a need in the art for alternative treatment protocols. Ex. 1002 at 283-284. Regeneron explained, however, that the claimed regimen was not *prima facie* obvious, and in fact, a 2012 paper by Heier et al demonstrated that dosing less frequently than every month was surprisingly noninferior to monthly dosing. *See infra* Sections VII.B.1, VII.C.3.

balancing the evidence of unexpected results."). Here, because Petitioner utterly fails to address the Examiner's consideration of the unexpected results that eventually led to the issuance of the '345 Patent, Petitioner has failed to meet its burden under *Advanced Bionics* step two.

Because the same or substantially the same art and arguments were previously presented to the Office and were considered by the Examiner, and Petitioner has failed to show that the Office materially erred in its consideration of that art or argument, the Board should exercise its discretion and deny institution under §325(d).

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

In a post-grant review proceeding, the Petitioner must "demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable." 35 U.S.C. § 324(a). And the Petition must "identif[y], in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim." *Id.*, § 322(a)(3). Where Petitioner fails to meet its threshold burden, the Board "may not authorize a post-grant review to be instituted." 35 U.S.C. § 324(a). Indeed, the Board denies institution where a petitioner has failed to demonstrate that at least one challenged claim is unpatentable. *See, e.g., One World Techs., Inc. v.*

Chervon (HK) Ltd., PGR2020-00059, 2020 WL 7222691 (Dec. 7, 2020); *Eton Pharms., Inc. v. Exela Pharma Scis., LLC*, PGR2020-00064, Paper 12 (Nov. 18, 2020); *Align Tech., Inc. v. 3Shape A/S*, PGR2018-00103, 2019 WL 2112182 (May 13, 2019). For the reasons discussed below, Petitioner has failed to "demonstrate that it is more likely than not that at least 1 of the" '345 Patent claims is unpatentable for Grounds 1, 2, and 3, and thus, denial of the petition is warranted. 35 U.S.C. § 324(a).

A. Ground 1: Petitioner Fails to Demonstrate That It Is More Likely Than Not That At Least One of the Challenged Claims Is Anticipated

Petitioner fails to show that any challenged claim is more likely than not unpatentable for anticipation based on Shams (Ground 1).

Shams (Ex. 1004) is a Genentech patent application that published on May 4, 2006 and was abandoned. The Shams specification discloses a single prophetic example, Example 1, that corresponds to a study that Genentech conducted with its VEGF antibody fragment, Lucentis® (ranibizumab), called PIER. Ex. 2002 ¶ 29-30. The PIER trial began in August 2004 and was completed in March 2007, nearly a year after Shams was published. Ex. 2010. The purpose of the study was to "evaluate the efficacy and safety of ranibizumab administered monthly for three months and then quarterly" in subjects with AMD. Ex. 1026 at 1. As shown in Figure 2 of Shams, subjects would receive three monthly doses of ranibizumab

followed by doses every 3 months for a period of 24 months. Ex. 1004 at 32:8-13. Shams does not include any data, nor does it report any results.

1. Petitioner Fails to Demonstrate That Shams' Treatment Schema Discloses the Recited Fusion Protein

Claim 1 requires using a VEGF antagonist that is a "receptor-based chimeric molecule comprising an immunoglobin-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." Ex. 1001 at 21:65-22:54. The Petition asserts that Shams discloses this limitation, but provides no support whatsoever for this proposition. Paper 2 at 31. It relies on the "treatment schema" shown in Figure 2, which Petitioner repeatedly depicts in the Petition. Paper 2 at 26-28, 31, 33, 38. The treatment schema, however, only shows a prospective method of treatment using ranibizumab, an antibody fragment, not a VEGF antagonist fusion protein as required by the claims of the '345 Patent.[15] That method of treatment does not anticipate the '345 Patent claims.

The Petition argues that Shams teaches that the treatment schema of Figure 2 could be used with any VEGF antagonist "includ[ing] Regeneron's fusion protein."

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[15] Even for ranibizumab, Shams merely discloses its plan to assess the efficacy and safety of administering ranibizumab according to the Figure 2 treatment schema, but says nothing about the treatment schema actually being effective.

Paper 2 at 31-32. But nothing in the "treatment schema" of Figure 2, on which Petitioner relies, states that one should use that schema with "VEFG-Trap (Regeneron)." The only compound Genentech identifies for evaluation in Figure 2 is its own ranibizumab. Ex. 1004 at 31-34, Fig. 2. And even for ranibizumab, Shams merely discloses a prophetic plan to assess ranibizumab using the Figure 2 treatment schema.[16] Figure 2 says nothing about treating angiogenic eye disorders with a fusion protein, let alone the specific type of "receptor-based chimeric molecule" required by the '345 Patent, using the Figure 2 treatment schema. To the contrary, as discussed *infra*, Shams expressly discloses that anti-VEGF antibodies are preferred, and that ranibizumab in particular, an antibody fragment, is the most preferred VEGF antagonist disclosed by Shams. Ex. 1004 at 7:6, 13-14. The VEGF antagonist fusion protein molecules required by the claims of the '345 Patent are not antibodies or antibody fragments. *See infra*. Thus Shams not only fails to disclose the claimed dosing method using a VEGF antagonist fusion protein as required by

[16] Petitioner disingenuously suggests that Groups 1, 2, and 3 depicted in Shams' Figure 2 treatment schema "received" a 0.3 mg dose 0.5 mg, or sham injection. Paper 2 at 26. However, Shams does not report any actual administration and its sole example, Example 1, is a prophetic example drafted in present tense. *See* Ex. 1004 at 31:1-19.

the claims, but it teaches that such molecules are the least preferred to use in any treatment method.

For this reason alone, Petitioner fails to carry its burden to show that Shams anticipates.

2. Petitioner Fails to Demonstrate That Shams' Reference to "VEGF-Trap (Regeneron)" Discloses the Recited Fusion Protein

Petitioner also fails to show that Shams expressly or inherently discloses the VEGF antagonist fusion protein recited in Claims 1-11 of the '345 Patent. Petitioner relies on Shams' reference to a "VEGF-Trap (Regeneron)" as allegedly disclosing use of a "receptor-based chimeric molecule" meeting the specific molecular requirements of the '345 Patent claims. The Petition fails to satisfy its burden of proving any aspect of this empty assertion. There is no evidence that "VEGF-Trap (Regeneron)" refers to any particular molecule, nor is there evidence that the term refers to a category of molecules that necessarily satisfies the requirements of the claims of the '345 Patent.

Petitioner does not even attempt to meet its burden of explaining what the term "VEGF-Trap (Regeneron)" denoted to a skilled artisan at the time of filing. Nothing in Shams discloses the amino acid sequence or component parts of "VEGF-Trap (Regeneron)," nor does it identify any references that provide this information.

Instead, the Petition asserts that the term "VEGF-Trap (Regeneron)" discloses a genus of compounds that "includes" compounds that satisfy the specific VEGF antagonist fusion protein limitations of the '345 Patent claims. Paper 2 at 31 ("One of skill in the art in 2006 would understand that 'VEGF Trap (Regeneron)' includes Regeneron's fusion protein, which, in 2006, included 'a receptor-based chimeric molecule comprising an immunoglobin-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.'") (citing Ex. 1003 ¶89). Notably, paragraph 89 of Dr. Wu's declaration (Petitioner's cited support) relies on the '345 patent itself (Ex. 1001), ***and not on Shams*** to purportedly evidence this limitation. Thus, Petitioner fails to show that a POSA would have understood Shams' reference to "VEGF Trap (Regeneron)" to be the recited fusion proteins of Claim 1. Shams therefore fails to identify by name or otherwise a single molecule satisfying the requirement of the '345 Patent claims and, at best, discloses a vast sea of molecules that ***could*** include chimeric molecules comprising the specific domains of a VEGF receptor specified by the '345 Patent claims, but could also include molecules that do not.

Indeed, as of January 2011, a POSA would have known that there were numerous Regeneron VEGF-Trap molecules, including many that do not satisfy the requirements of the '345 Patent claims. By the early 2000s, Regeneron had developed, tested and published on a variety of engineered VEGF fusion proteins

that it called "VEGF Trap" molecules. For instance, a 2002 PNAS article published by Holash *et al.*[17] describes a number of different Regeneron's VEGF-Traps, many of which fall outside of the scope of the '345 Patent claims. Ex. 2011 at 1.[18] Likewise, by 2006, a Regeneron published patent application to Daly *et al.*, PCT/US2004/021059, titled "VEGF Traps and Therapeutic Uses Thereof," discloses multimeric VEGF-binding proteins comprising two or more fusion polypeptides (also called VEGF 'trap' molecules), which include molecules that fail

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[17] Petitioner acknowledges that Holash 2002 was in the prior art since it relies on this publication as a ground for challenge in its concurrently filed IPR challenging Regeneron Patent No. 10,464,992 in IPR2021-00402, Petition at 4.

[18] Holash discloses that VEGF $Trap_{parental}$ was created by fusing the first three Ig domains of Flt1 (VEGFR1) to the Fc region; VEGF-$Trap_{\Delta B1}$ was created by removing a highly basic 10-aa stretch from the third Ig domain of the parental VEGF-Trap; and VEGF-$Trap_{\Delta B2}$ was created by removing the entire first Ig domain from VEGF-$Trap_{\Delta B1}$. *Id.* None of these disclosed VEGF-Traps, which contain only domains of VEGF receptor 1 and no domains from VEGF receptor 2, satisfies the fusion protein limitation of the '345 Patent claims.

to satisfy the compound requirements of the '345 Patent claims.[19] Thus, a POSA would not have understood Shams' disclosure of "VEGF-Trap (Regeneron)" — a genus of fusion proteins — to necessarily satisfy the recited fusion protein limitation of '345 Patent, Claim 1.

As the Federal Circuit has explained, a prior art reference may anticipate without disclosing a feature of the claimed invention only "if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

The mere possibility that "VEGF-Trap (Regeneron)" could comprise a chimeric fusion protein molecule meeting the limitation of Claim 1 is insufficient to demonstrate inherency for anticipation. *See Amgen, Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, at 24-25 (Aug. 30, 2019) (rejecting inherent anticipation where "eculizumab" referred to at least two different proteins in the prior art,

[19] Daly discloses that VEGF-traps can include receptor components from VEGFR3 (Flt-4), which fall outside the requirements of the '345 Patent claims. Ex. 2012 at [002].

including the unclaimed "Thomas IgG4 isotype eculizumab"); *see also Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) (finding incomplete prior art disclosure of a composition insufficient to inherently disclose the claimed composition).

Shams' recitation of a generic "VEGF-Trap (Regeneron)" does not expressly or inherently disclose a method of treating an angiogenic eye disorder using the recited VEGF antagonist fusion protein of the challenged claims. Disclosure of a method of using a genus of compounds does not anticipate a method of using one compound from that genus. *See Impax Lab'ys, Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006). Thus, Petitioner has failed to show that Shams anticipates the challenged claims.

3. Shams Does Not Disclose the '345 Patented Invention As Arranged in the Claims

To anticipate, a reference "must not only disclose all elements of the claims within the four corners of the document, but must also disclose those elements arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (internal quotations omitted). Petitioner fails to show that the disclosures in Shams upon which it relies are arranged as in the challenged claims of the '345 Patent.

Petitioner picks and chooses from different portions of the Shams' specification and different embodiments without identifying any language tying

them together into a single, coherent disclosure of an anticipating method. For the claimed dosing regimen — "a single initial dose" followed by "secondary dose[s] … administered 4 weeks after the immediately preceding dose" followed by "tertiary dose[s] … administered 12 weeks after the immediately preceding dose," (Ex. 1001 at Claim 1) — Petitioner relies on Figure 2 of Shams, which illustrates the prophetic dosing regimen of Example 1. *See* Paper 2 at 30-38.

But, as explained above, because Example 1 and Figure 2 specifically disclose administering ***ranibizumab***, which does not satisfy the '345 claims, the Petitioner is forced to cherry-pick from Shams' laundry list of "VEGF antagonists" to find one that is purportedly recited by the claims. *See* Paper 2 at 31.

"VEGF antagonists," according to Shams, refers to a wide range of molecules — any "molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with VEGF activities." Ex. 1004 at 6:27-29. These "include anti-VEGF antibodies" as well as "antigen-binding fragments" of such antibodies, "receptor molecules" and their "derivatives," "anti-VEGF receptor antibodies" and various "VEGF receptor antagonists" including "VEGFR tyrosine kinase inhibitors." Ex. 1004 at 6:29-33. The term also includes "antagonist variants of VEGF, antisense molecules directed to VEGF, RNA aptamers specific to VEGF, and ribozymes against VEGF or VEGF receptors." *Id.* at 6:33-7:1. None of these constitute the

specific type of "receptor-based chimeric molecule" required by the '345 Patent claims.

Shams lists numerous examples of its preferred antibodies, none of which can be used to practice the '345 Patent claims, including A4.6.1, bevacizumab, ranibizumab, G6, B20, 2C3 "and others as described in" ten references Shams identifies. *Id.* at 7:8-13. And "[m]ore preferably," of all the disclosed anti-VEGF antagonists, is ranibizumab — the undisputed focus of Shams. *Id* at 7:13-14.

Shams' disclosure of "VEGF-Trap (Regeneron)" appears but once in Shams and only among an extensive list of VEGF antagonists. "VEGF-Trap (Regeneron)" is not among the most preferred or even the preferred VEGF antagonists on this list. Shams makes clear that "anti-VEGF antagonistic antibodies" are to be preferred over the other categories of disclosed VEGF antagonists. Ex. 1004 at 7:6. The '345 Patent, however, does not claim the use of any antibodies. Petitioner does not attempt to explain why a POSA would select the disfavored "VEGF-Trap (Regeneron)" molecules from among all the possible VEGF antagonists disclosed in Shams and then, from among those "VEGF-Trap (Regeneron)" molecules known in the prior art, select a particular type, as required by the '345 Patent claims, that was never even disclosed by Shams. Thus, Shams discloses "VEGF-Trap (Regeneron)" molecules only as a small, disfavored portion of a much larger genus of VEGF antagonists. *See Impax Lab'ys*, 468 F.3d at 1383 (finding no anticipation of method

of using riluzole because "riluzole is just one of hundreds of compounds included in formula I" of the prior art patent).

Even if Shams had specifically called out "VEGF-Trap (Regeneron)" as the molecule to use in Figure 2 — instead of relegating it to the non-preferred backwater of a vast genus of VEGF antagonists — Petitioner points to nothing in Shams to suggest that a "VEGF-Trap (Regeneron)" molecule (let alone the precise type of fusion protein required by the '345 Patent claims) could simply be substituted into the dosing protocol set forth in Shams Figure 2. Petitioner points to no disclosure in Shams to suggest a corresponding dose or dosing regimen for a "VEGF-Trap (Regeneron)" molecule. Petitioner's attempt to rewrite Shams' Example 1 and Figure 2 to replace its single-minded focus on "ranibizumab" with "VEGF-Trap (Regeneron)" (*Id.*; Ex. 1004 at 6:33) is not supported by the disclosure of Shams or the law of anticipation.

The Federal Circuit and its predecessor court have explained that anticipation requires more than merely picking and choosing from a single prior art reference to arrive at a claimed invention. *See Net MoneyIN*, 545 F.3d at 1371 (finding that district court erred in "combin[ing] parts of the separate [examples] shown in the … reference" to conclude that a challenged claim was anticipated because "it is not enough that the prior art reference … includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed

invention."); *In re Arkley*, 455 F.2d 586, 587-88 (CCPA 1972) (A "reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [claimed invention] without ***any*** need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference. Such picking and choosing … has no place in the making of a 102, anticipation rejection.") (emphasis in original).

The Board has also repeatedly denied institution where an allegedly anticipatory reference does not disclose the claim elements as they are arranged in the challenged claim. For example, in *Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, the Board denied institution because the allegedly anticipatory reference required "picking and choosing with no guidance in the prior art" to arrive at the claimed invention. IPR2017-00822, 2017 WL 3974063, at *6 (Sept. 7, 2017) (rejecting the petitioner's argument that a POSA "reading the [PCT] would 'at once envisage' the claimed arrangement or combination" because the PCT did not "teach each of the limitations of the challenged claims arranged as in the claims"); *see also Endo Pharms. Inc. v. Depomed, Inc.*, IPR2014-00655, 2014 WL 4925714, at *7 (Sept. 29, 2014) (denying institution because "Petitioner cannot combine parts of separate embodiments disclosed in the [reference] to piece together the claimed invention."); *see also Reckitt Benckiser LLC v. GEMAK Tr.*, IPR2020-00184, 2020 WL 2511249 (May 15, 2020).

As in *Coherus Biosciences*, Shams discloses a broad genus of proteins and there is nothing in Shams directing a POSA to use "VEGF-Trap (Regeneron)" over any other disclosed VEGF antagonist. *See, e.g.*, *Coherus Biosciences Inc.*, 2017 WL 3974063, at *7 (denying institution where the allegedly anticipatory reference "provides innumerable possibilities for proteins that may provide sufficient buffering capacity" and the recited protein is not identified "in any example or as a preferred antibody."). As the Board explained in *Coherus BioSciences*, "picking and choosing with no guidance in the prior art as to which choices to make is not anticipation." 2017 WL 3974063, at *6.

Because Petitioner has done no more than piece together different disclosures from separate embodiments in Shams to argue anticipation, the Board should decline to institute Petitioner's Ground 1 anticipation challenge.

4. Petitioner Fails to Show That Shams Discloses or Enables A Therapeutically Effective Method of Treating an Angiogenic Eye Disorder

Claim 1 of the '345 Patent requires a therapeutically effective method for treating an angiogenic eye disorder. *See supra* Section IV.A. Petitioner relies on Shams' disclosure of a prophetic dosing regimen for ranibizumab in Example 1 and Figure 2 ("Treatment Schema") for its anticipation challenge. However, Shams' disclosed 12-week dosing regimen was a failure. A prior art reference cannot anticipate a claimed invention "if the allegedly anticipatory disclosures

cited as prior art are not enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003); *see also United States v. Adams*, 383 U.S. 39, 50 (1966) (finding that an invention that is inoperable or fails to achieve its intended result does not anticipate). In addition, a POSA would not have viewed Shams as disclosing an effective method for treating an angiogenic eye disorder in a patient. Because Shams is not enabled and does not disclose a recited claim limitation — ***treatment*** of an angiogenic eye disorder — Shams does not anticipate the '345 Patent claims.

a. Petitioner is Not Entitled to a Presumption that Shams' Disclosure of a 12-Week Dosing Regimen Is Enabled

The Petition presents no evidence that Shams discloses an ***effective*** quarterly dosing regimen. Shams itself does not supply this evidence as it discloses only a prophetic quarterly dosing regimen. Nor can Petitioner rely on a presumption of enablement to cure this deficiency because Shams is not an issued patent.

While disclosures of prior art patents enjoy a presumption of enablement in adversarial proceedings, the Federal Circuit has not held that this same presumption applies to non-patent printed publications. *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 661 n.10 (D. Del. 2014). Indeed, this presumption should ***not*** to apply to non-patent printed publications. Issued patents are presumed valid because of "the basic proposition that a government agency such as the [PTO] was presumed to do its job." *Am. Hoist & Derrick Co. v. Sowa*

& Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984). Patent prosecution is an "inquisitorial process between patent owner and examiner," *see SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018), which provides a level of confidence that the patent examiner has performed his or her job in issuing a patent. There is no such "inquisitorial process" for non-patent prior art publications, especially as to whether a disclosure was enabled.

In a PGR proceeding, Petitioner bears the burden to demonstrate that it is "more likely than not" that at least one of the challenged claims is unpatentable. 35 U.S.C. § 324(a). Such an adversarial proceeding presents different prudential considerations from patent prosecution[20] and thus the burden to make a *prima facie*

[20] The burden of proving non-enablement of an allegedly anticipating reference in prosecution is on the patent applicant, who "is in a better position to show, by experiment or argument, why the disclosure in question is not enabling or operative" because "an examiner, who has no access to experts or laboratories, is not in a position to test each piece of prior art for enablement in citing it, and requiring him to do so would be onerous, if not impossible." *In re Antor Media Corp.*, 689 F.3d 1282, 1288-89 (Fed. Cir. 2012). But this rationale does not extend to adversarial PGR proceedings where a Petitioner has the resources and

case of anticipation — including the enablement of an allegedly anticipatory non-patent reference — should be placed firmly on the Petitioner seeking to invalidate an already issued patent. *See e.g.*, *Takeda Pharm. Co., Ltd v. Handa Pharms., LLC*, No. C-11-00840 JCS, 2013 WL 9853725, at *64-65 (N.D. Cal. Oct. 17, 2013) (concluding that the ultimate burden of proving enablement of allegedly anticipatory non-patent prior art is on the patent challenger).

Just as Petitioner bears the initial burden for establishing the "printed publication" status of a prior art reference at the institution stage by identifying "evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent," *see Hulu*, IPR2018-01039, Paper 29 at 16, so too here, to satisfy its threshold burden under 35 U.S.C. § 324(a), Petitioner should bear the burden to come forward with evidence that the allegedly anticipatory disclosures of Shams are enabled. Petitioner has made no such showing.

Moreover, the factual record, including the prosecution history of Shams, evidences that no such presumption is appropriate here. Ex. 2013; Ex. 2014. Shams' disclosure and claims were repeatedly rejected during prosecution for lack

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wherewithal to develop evidence, using experts and laboratories, to show enablement of non-patent prior art.

of written description and enablement; these objections were never overcome and Shams was ultimately abandoned.[21] Ex. 2013; Ex. 2014. Thus, the basic rationale for a presumption of enablement of an issued patent should not apply to non-patent prior art publications and, indeed, is counterfactual in the case of Shams.

b. Overwhelming Evidence Demonstrates That Shams Was Not a Therapeutically Effective Method for Treating an Angiogenic Eye Disorder

Shams' disclosure of a prophetic quarterly (q4/q12) dosing regimen for ranibizumab corresponds to and was tested in Genentech's Phase IIIb clinical trial called the "PIER Study." Ex. 2002 ¶¶ 27, 29-30; *see also* Ex. 2001 ¶¶ 63-64. Genentech's PIER clinical trial results, and publications reporting on those results, show that Shams' disclosed 12-week dosing regimen for ranibizumab was a failure and not an effective method for treating an angiogenic eye disorder in a patient.

The PIER study was designed to test whether ranibizumab (Lucentis) could be dosed quarterly rather than monthly and still maintain its efficacy. Ex. 1026 at 1; Ex. 2015 at 1; Ex. 2002 ¶ 27. Patients in PIER were randomized to receive 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham control by intravitreal injections

[21] Shams (Ex. 1004) was the priority utility filing leading to U.S. continuation applications S.N. 11/738, 284, S.N. 13/780,239, and 14, 307,233 (which never published), all of which were abandoned.

administered monthly for the first three months followed by quarterly injections (every 12 weeks) through month 24 of the study. Ex. 1026 at 2.

In the first year of PIER, patients in the treatment arm gained visual acuity during the first three monthly injections of ranibizumab, but then lost all visual acuity gains after moving to fixed quarterly dosing. Ex 1026 at 7; Ex. 2002 ¶ 31; Ex. 2001 ¶ 65. This vision loss was accompanied by anatomic changes, such as increase in vascular leakage and mean retinal thickness, that are hallmark characteristics of recurrence of wet AMD. Ex. 2002 ¶ 32.

While patients in PIER were losing vision, Genentech announced results from its pivotal Phase III ANCHOR and MARINA trials that showed that fixed monthly doses of ranibizumab could improve visual acuity, and maintain those vision improvements over the course of treatment. Ex. 2002 ¶¶ 17-24. After MARINA and ANCHOR results were made public, it was no longer considered appropriate or ethical treatment to simply permit the progression of a patient's wAMD (as was done with sham control). Ex. 2002 ¶¶ 20, 23, 33; Ex. 2001 ¶ 69-70. As a consequence, the PIER protocol was amended to allow sham control subjects to cross over to the treatment arm of monthly dosing of 0.5 mg ranibizumab for the remaining year of the study. Ex. 1026 at 2; Ex. 2002 ¶ 33; Ex. 2001 ¶ 66, 69.

It is not merely the case that the PIER regimen was less effective at improving visual acuity as compared to a monthly regimen; following the monthly loading doses, quarterly injections in PIER led to vision loss, with ultimately ***zero*** gains in visual acuity as compared to baseline. Ex. 1026 at 5 (Figure 1). The one-year PIER results were so disappointing that Genentech amended the PIER study protocol yet again —this time to allow ***all patients*** remaining in the study the opportunity to roll over from the ***12-week (quarterly) dosing*** to receive 0.5 mg ranibizumab ***monthly dosing*** for the remainder of the two-year study. Ex. 2016 at 2; Ex. 2002 ¶ 34; Ex. 2001 ¶ 66. The fact that Genentech amended its PIER Study protocol to allow the quarterly treatment arm to roll-over to monthly dosing was an acknowledgement that PIER quarterly dosing regimen did not work. Ex. 2002, ¶ 34; Ex. 2001 ¶ 66, 69.

The PIER study was recognized as a failure in the art. Ex. 2002 ¶¶ 35-38, 43; Ex. 2001 ¶¶ 68, 70. Genentech presented PIER's One Year results in late May/early June 2006 at the Retinal Physician Symposium. Ex. 2002 ¶ 31; Ex. 2015 at 1. Dr. David Brown, the PIER investigator who first presented the data, said it was "a shock to a lot of people" that patients in the PIER study did not maintain the improvements that were seen in the MARINA and ANCHOR trials. Ex. 2017 at 2. Dr. Brown noted PIER's key take-away: "This shows that we cannot just mandatorily treat on a quarterly basis and maintain the visual gains

seen with the first three monthly injections." Ex. 2017 at 1; Ex. 2002 ¶ 37. In fact, industry publications reported: "The PIER data have led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing." Ex. 2015 at 1. Indeed, as discussed in Section VII.B. below, PIER was not only regarded as a failure in the art, but also as a cautionary tale against fixed quarterly dosing.

Because Petitioner has failed to show that Shams enabled or discloses a therapeutically effective method of treating an angiogenic eye disorder, Shams cannot anticipate.

5. Shams Fails to Disclose A Tertiary Dose That Maintains the Therapeutic Effect Throughout the Course of Treatment When Administered 12 Weeks After the Immediately Preceding Dose

Claim 1 requires a tertiary dose that maintains therapeutic effect when administered 12 weeks after the immediately preceding dose. *Supra*, pp. 10-12. But Shams' dosing regimen failed to maintain a therapeutic benefit during the quarterly dosing phase of the regimen. *Supra*, pp. 62-64.

As noted in Section VI.4.3. above, when the Shams treatment schema of Figure 2 was tested in the PIER Study, all visual acuity gains from the first three monthly doses of ranibizumab were lost once injections were reduced to quarterly (12-week) administration. Ex. 1026 at 5 (Figure 1). As discussed above, the PIER

Study was a failure and was consistently characterized as an ineffective treatment regimen in the art.

Because Petitioner has failed to show that Shams discloses "a tertiary dose that maintains a therapeutic effect throughout the course of treatment when administered 12 weeks after the immediately preceding dose," Petitioner has failed to make its threshold showing for Ground 1.

B. Ground 2: Petitioner Fails to Demonstrate That It Is More Likely Than Not That At Least One of the Challenged Claims Is Obvious

According to the Petition, the 2009 Press Release in view of Shams renders the '345 Patent claims obvious. Not so.

As a threshold matter, Petitioner fails to address, let alone overcome, Regeneron's showing during prosecution that the claimed dosing regimen exhibits unexpected results. This omission is fatal to Petitioner's obviousness argument. To make matters worse, neither the 2009 Press Release nor Shams teaches an ***effective*** method of treating an angiogenic eye disorder with a quarterly dosing regimen of the recited VEGF antagonist. Nor does either provide a reasonable expectation of success for achieving an effective method of treatment. To the contrary, Shams' quarterly dosing regimen with Lucentis was an acknowledged failure. Accordingly, Petitioner has failed to "demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable," and thus, denial of the petition is warranted. 35 U.S.C. §§ 322(a)(3), 324(a).

1. The Board Should Deny Institution Under 35 U.S.C. § 324(a) Because Petitioner Has Failed to Address, Let Alone Overcome, the Examiner's Finding of Unexpected Results

As discussed in the Petition, during prosecution, Regeneron overcame an obviousness-type double patenting rejection based on unexpected results demonstrating that extended dosing of aflibercept was noninferior to the existing therapy, which as of the priority filing date of the 345 Patent, was fixed monthly doses of ranibizumab. Ex. 1002 at 255. To overcome an obviousness-type double patenting rejection during prosecution, Regeneron relied on a 2012 paper by Heier *et al.* (Ex. 1012) to demonstrate that with extended dosing, *i.e.*, dosing less frequent than monthly, "it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible." *Id.* at 256. Based on Regeneron's response, the Examiner withdrew the obviousness-type double patenting objection (*id.* at 225-226) and later allowed the claims. *Id.* at 145-46.

Although Petitioner acknowledges that Regeneron presented evidence of unexpected results during prosecution (*see, e.g.*, Paper 2 at, 36, 60, 62), nowhere does the Petition overcome, or even substantively address, these arguments. This omission is fatal to Petitioner's Ground 2. The Board has consistently denied institution where a petitioner fails to address secondary indicia of non-obviousness, such as unexpected results, in the prosecution history. *See, e.g., Coalition for*

Affordable Drugs V LLC v. Hoffmann-La Roche Inc., IPR2015-01792, Paper 14 at 18 (Mar. 11, 2016) (denying institution because "the unrebutted objective indicia of nonobviousness presented in the prosecution history of the [challenged] patent … supports the non-obviousness of the challenged claims" and "[t]he Petition … should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success on the merits."); *see also Omron Oilfield & Marine, Inc. v. MD/Totco, a division of Varco, L.P.*, IPR2013-00265, Paper 11 at 16 (Oct. 31, 2013) (denying institution where Petitioner did not in its Petition challenge the merits of commercial success evidence Patent Owner developed in reexamination involving different prior art references than those asserted in IPR); *see Gilead Scis., Inc. v. United States*, IPR2019-01453, Paper 14 at 30 (Feb. 20, 2020) (finding that "Petitioner's failure to persuasively address [the showing of unexpected results during prosecution] in the Petition means that Petitioner falls short of its burden to establish a reasonable likelihood of success in prevailing on its challenge"); *Stryker Corp. v. KFX Med., LLC*, IPR2019-00817, Paper 10 at 29 (Sept. 16, 2019) (finding Petitioner's "failure to address the known evidence of secondary considerations" in a related proceeding "weighs in favor of denying institution"); *Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, Paper 15 at 23-24 (Mar. 22, 2017) ("We have cautioned petitioners in prior proceedings that known evidence of secondary considerations should be addressed in the petition.").

Here, Petitioner fails to address Regeneron's showing of unexpected results during prosecution. The only reference to Regeneron's showing of unexpected results in the Petition is an ***acknowledgment*** by the Petitioner that Regeneron put forth evidence of unexpected results during prosecution. *See, e.g.* Paper 2 at 36 ("Heier (which Patent Owner cited as evidence of 'unexpected results' during prosecution) …"); *see also id.* at 60, 62. At least in *Coalition for Affordable Drugs* and *Omron Oilfield & Marine*, the petitioners ***attempted***, albeit insufficiently, to overcome the record evidence of objective indicia of non-obviousness. Here, where Petitioner has utterly failed to address Regeneron's showing of unexpected results, the Board should decline to institute for the same reasons it declined to institute in *Coalition for Affordable Drugs* , *Omron Oilfield & Marine*, *Gilead Scis.*, *Stryker Corp.* and *Robert Bosch Tool Corp.*

2. A POSA Would Not Reasonably Expect to Treat an Angiogenic Eye Disorder Using the Claimed Regimen by Combining the 2009 Press Release and Shams

Petitioner argues that the '345 Patent claims are rendered obvious by the 2009 Press Release in view of Shams. But a claim is not rendered obvious "merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Rather, Petitioner must "demonstrate … that the skilled artisan would have had a reasonable expectation of success in" "combin[ing] the teachings of the prior art references." *Intelligent Bio-*

Sys., Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1367-68 (Fed. Cir. 2016); *see also KVK-Tech, Inc. v. Shire PLC*, IPR2018-00290, 2019 WL 2884463, at *7 (July 3, 2019) (same).

Petitioner fails to show that a POSA would have had a reasonable expectation of success in treating an angiogenic eye disorder with the claimed dosing regimen by combining the 2009 Press Release and Shams. In Ground 2, Petitioner relies on Shams for the tertiary dosing limitation only because Shams discloses "tertiary doses every three months" with ranibizumab. Paper 2 at 48. In Petitioner's own words, it is "merely combin[ing] prior art elements (Shams' 12-week dosing) to a known method (the 2009 Press Release's 4-week secondary dosing plus 12-week tertiary dosing) to arrive at a predicate result." Paper 2 at 49.

But the Board has denied institution where a petitioner fails to make a threshold showing that a POSA would have had a reasonable expectation of success in combining asserted prior art references to achieve the claimed invention. *See, e.g.*, *Thermo Fisher Sci. Inc. v. Regents of the Univ. of Calif.*, IPR2018-01156, 2018 WL 6318146, at *10 (Dec. 3, 2018) (declining to institute review "[b]ecause an obviousness argument cannot succeed without Petitioner establishing a reasonable likelihood that a person of ordinary skill in the art would have had a reason to combine the relevant references" and "demonstrating that each of [a claim's] elements was, independently, known in the prior art" is not sufficient) (quoting *KSR*

Int'l, 550 U.S. at 403 (internal quotation marks omitted); *see also Illumina, Inc. v. Complete Genomics, Inc.*, IPR2020-00079, Paper 7 (Apr. 22, 2020) (denying institution in part because petitioner failed to "sufficiently show[] that one of ordinary skill in the art would have had a reasonable expectation of success"); *NOF Corp. v. Nektar Therapeutics*, IPR2019-01392, Paper 23 (Feb. 4, 2020) (same). Without demonstrating that a POSA would have had a reasonable expectation of success in treating an angiogenic eye disorder using the claimed dosing regimen, Petitioner fails to demonstrate that the '345 Patent claims are obvious.

Not only does Petitioner fail to make the requisite showing for a reasonable expectation of success, but it is clear that a POSA would ***not*** have had a reasonable expectation of success in treating an angiogenic eye disorder with the claimed dosing regimen based on the 2009 Press Release and Shams.

First, the 2009 Press Release does not disclose an effective method for treating an angiogenic eye disorder using a quarterly tertiary dosing regimen. In the 2009 Press Release, Regeneron announced that it had completed enrollment in two randomized, double-masked Phase III clinical trials, called VIEW 1 and VIEW 2, evaluating "VEGF Trap-Eye" for the treatment of wet AMD. Ex. 1005 at 1. The Press Release reported that the first year of the VIEW studies would involve dosing patients with VEGF Trap-Eye either monthly or every two months, after three monthly doses, and in the second year "patients will continue to be followed and

treated for another year on a flexible, criteria-based extended PRN [*pro re nata* — taken as needed] regimen with a dose administered at least every 12 weeks, but not more often than every four weeks until the end of the study." *Id.*

Notably, the Press Release does not disclose that any patient was dosed, nor does it disclose that any patient had started the second year of PRN dosing. *Id.* Additionally, the Press Release does not report any results but does report that "[o]ne-year primary endpoint data from both studies are expected in the fourth quarter of 2010." *Id.* Thus, not only does the 2009 Press Release fail to disclose quarterly dosing — which Petitioner acknowledges, Paper 2 at 48; Ex. 1003 ¶ 108 — but it does not disclose the ***treatment*** of any angiogenic eye disorder with any dosing regimen. The 2009 Press Release discloses a ***prospective*** study, for which enrollment is complete.[22] Accordingly, the 2009 Press Release does not disclose

[22] The Petition incorrectly suggests that the 2009 Press Release reports on a study that has been completed: "The 2009 Press Release teaches, among other arms, 'that patients ***received*** intravitreal doses of 0.5 mg or 2g VEGF Tap-Eye [sic] at 4–week intervals in the first year, ***followed*** by continual treatment for another year on a flexible, PRN regiment [sic], with a dose administered at least every 12 weeks.'" Paper 2 at 42 (emphases added). Although the statement includes a citation to the Press Release, the quoted language is not found in the Press Release.

treatment of any disease. In fact, results from the first year of the study were not even expected until "the fourth quarter of 2010," over a year after the publication of the Press Release. Moreover, the 2009 Press Release does not make any statements about the efficacy of VEGF-Trap-Eye. Nor could it. Indeed, FDA prohibits pre-approval promotion of investigational drugs. 21 C.F.R. § 312.7(a) ("A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug."). Accordingly, a POSA would not have understood the disclosure or announcement of a prospective Phase III trial to provide a reasonable expectation of success.

Second, a POSA would not have had a reasonable expectation of success in combining the 2009 Press Release and Shams to achieve the claimed treatment regimen because a POSA would have recognized that the 12-week ranibizumab

dosing regimen disclosed in Shams would not treat an angiogenic eye disorder.[23] Petitioner argues that "[i]t would have been natural for one of skill in the art to look at Shams' teachings when considering the 2009 Press Release's 4 + 8 week dosing …." Paper 2 at 48. But Petitioner does not demonstrate that a POSA would

[23] Petitioner asserts that "success was predictable because Shams teaches a successful 4 + 12 week dosing regimen…" (Paper 2 at 49-50) but fails to cite evidence to support this assertion. Moreover, as detailed in Ex. 2002 (¶¶ 29-43) and Ex. 2001 (¶¶ 63-70), Shams' 4 +12 week dosing regimen was a failure and recognized as such in the art. Petitioner also asserts that "Regeneron publicly announced that VEGF Trap was successful in quarterly doses" and cites paragraph 114 of Dr. Wu's declaration in support. Paper 2 at 50 & n.148. But Dr. Wu's testimony does not support a finding of obviousness. *First*, Dr. Wu's declaration at paragraph 114 does not appear to be cite the correct document (Ex. 1030, not Ex. 1031). Regardless, neither Exhibit is properly cited in the Petition. *Second*, even if Petitioner had properly cited Exs. 1030 and 1031, these documents merely purport to provide results for patients who received ***a single dose*** of VEGF Trap Eye, not the claimed dosing regimen. Reported success after a single administration does not render obvious the claimed dosing regimen.

have had a reasonable expectation of success in combining Shams with the 2009 Press Release to achieve an effective treatment regimen, nor could it.

As discussed *supra*, Shams' prophetic disclosure of a quarterly dosing regimen for ranibizumab was tested in Genentech's PIER trial, which was widely-regarded as a failure. *See supra* Section VII.A.4. Moreover, following the disclosure of PIER clinical trial results, peer-reviewed publications reflect the perception that fixed quarterly dosing and even fixed extended dosing should be approached with caution in view of the clinical results in PIER:

- "A recent analysis of the ANCHOR, MARINA, and PIER data demonstrated that monthly intravitreal ranibizumab dosing significantly reduced the frequency of macular hemorrhages... The effect was lost when patients were switched from monthly to quarterly dosing in the PIER study. ***Reducing the frequency of injections should, therefore, be done with caution***." Ex. 2018 at 5, emphasis added.

- "In the PIER trial, when patients were switched from monthly to quarterly injections of ranibizumab, they subsequently lost the vision they had gained with monthly injections." Ex. 2019 at 1.

- "In PIER, ***no benefit of ranibizumab over sham was observed after the patients were switched to the quarterly protocol***. … As seen in PIER, 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***." Ex. 2020 at 5, emphasis added.

- "However, fixed quarterly [citing PIER] or 'as needed' (pro re nata [PRM]) dosing regimens, without requiring monthly monitoring visits were not effective at maintaining vision." Ex. 2021 at 1.

After PIER, no retina physician would treat his or her wAMD patient with fixed quarterly dosing of ranibizumab. Ex. 2001 ¶ 70; Ex. 2002 ¶ 43.

Until Regeneron conducted its Phase III pivotal trials on aflibercept in wAMD, there remained an unmet need for extended dosing regimens of VEGF antagonists for the treatment of angiogenic eye disorders, despite "extensive efforts to decrease injection and monitoring frequency." Ex. 2021 at 9. Shams not only fails to provide a reasonable expectation that a fixed quarterly dosing regimen would work, but rather, is evidence of long-felt need and failure of others to develop such an extended dosing regimen. Simply put, a POSA would not have had a reasonable expectation of success in using quarterly dosing to treat angiogenic eye disorders and would have been discouraged by the results of the PIER study. Thus, Petitioner is incorrect to suggest that "Shams teaches a ***successful*** 4 + 12 week dosing regimen." Paper 2 at 49-50 (emphasis added).

Accordingly, neither the 2009 Press Release nor Shams, alone or together, would have provided a POSA with a reasonable expectation of success that a 12-week dosing regimen would work for the VEGF antagonists recited by the '345 Patent claims. Without more, merely plucking the tertiary quarterly dosing regimen from Shams and combining it with a prospective trial in the 2009 Press Release, does not render the '345 Patent claims obvious.

* * *

For the reasons discussed above, Petitioner has not met its burden under 324(a) and 322(a) to demonstrate that it is more likely than not that at least one claim will be found unpatentable as obvious over the 2009 Press Release in view of Shams. Accordingly, the Board should deny institution.

C. Ground 3: Petitioner Fails to Demonstrate That It Is More Likely Than Not That At Least One of the Challenged Claims Lacks Written Description

Claim 1, the only independent claim of the '345 Patent, requires that "each tertiary dose is administered 12 weeks after the immediately preceding dose." Ex. 1001 at Claim 1. Petitioner concedes that the "'345 patent mentions 12–week tertiary dosing." Paper 2 at 66. This "mention" also appears in the priority applications. Although Petitioner argues that the '345 Patent is invalid for lack of written description because it discloses too many different dosing regimens, Petitioner fails to meet its burden of demonstrating that it is more likely than not that at least one of the challenged claims lacks written description.

Petitioner does not cite any case invalidating claims merely because the specification discloses too many examples. Paper 2 at Sec. VIII. Instead, Petitioner relies on cases where the specification did not disclose the claimed embodiment and, at best, support could be found only by selectively piecing together portions of the specification with no blazemarks that pointed to the claimed embodiment. *Id.* at 65-71 (citing *Novozymes*, *Purdue Pharma L.P.*, *Ruschig*, *Fujikawa*, *FWP IP ApS*,

Boston Sci. Corp.). Those cases have no applicability to the '345 Patent because the priority applications here disclose as one example the precise embodiment covered by the claims. If a patent specification discloses multiple examples, and one of those examples is the claimed embodiment, as it is here, the claim is supported. *Erfindergemeinschaft UroPep v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 656 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (hereinafter "*UroPep*").

Accordingly, because the challenged claims are adequately supported by the specification, Petitioner has not demonstrated at least one of the challenged claims is unpatentable for lack of written description.

1. Petitioner Fails to Demonstrate That the Claims More Likely Than Not Lack Written Description Because the '345 Patent Specification Discloses as a Specific Example the Exact Dosing Regimen Claimed

Section 112 does not prescribe the manner in which a specification must support a claim, so long as the specification "clearly allow[s] persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original) (internal quotation marks omitted).

The Petitioner cannot carry its burden because the '345 Patent specification 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 ½, 9, 9 ½, 10, 10 ½, 11, 11 ½, ***12***, 12 ½, 13, 13 ½, 14, 14 ½, or more) ***weeks after the immediately preceding dose***." Ex. 1001 at 3:57-62 (emphases added). Accordingly, the '345 Patent specification specifically discloses that a "secondary dose is administered … 4 … weeks after the immediately preceding dose, and each tertiary dose is administered … 12 … weeks after the immediately preceding dose." *Id.* This is also known as a q4/q12 dosing regimen. Thus, the specification discloses the q4/q12 dosing regimen of Claim 1 as an "exemplary embodiment." *Id.* at 3:57. This exact same disclosure is found in the 2011 Provisional Applications to which the '345 Patent claims priority; therefore, there can be no doubt that the claims are supported by the 2011 Provisional Applications. *See* Ex. 1045 at [0016]; Ex. 1046 at [0016]; Ex. 1047 at [0016].

Petitioner argues that this disclosure is insufficient because the patent discloses other dosing regimens as well. Paper 2 at 68. A court addressing a very similar set of circumstances explained that "[a] patentee is free to selectively claim one particular embodiment without running afoul of the written description requirement." *UroPep*, 276 F. Supp. 3d at 656, *aff'd* 739 F. App'x 643. Indeed, "[i]t is common for patentees to disclose a range of possible embodiments" and "a patentee need not indicate that one embodiment is 'of special interest' in order to claim it." *Id.*

In *UroPep*, the patent claimed a method for prophylaxis or treatment of benign prostatic hyperplasia (BPH) with a phosphodiesterase (PDE) 5 inhibitor. *Id.* The patent challenger argued that the written description was not sufficient because the specification described other PDE inhibitors, such as PDE1 and PDE4 inhibitors, as well as using all three PDE inhibitors (PDE1, PDE4, and PDE5) to treat BPH; and the specification taught the treatment of other prostatic diseases. *Id.* at 655. Thus, the challenger argued that the specification lacked written description because it did not provide blazemarks leading one specifically to the treatment of ***BPH*** with a ***PDE 5*** inhibitor. *Id.* at 655. But, because "selectively claim[ing] one particular embodiment" does not "run[] afoul of the written description requirement," the court found the claims not invalid for lack of written description. *Id.* at 656.

Petitioner does not cite a single case that runs counter to *UroPep*, invalidating or rejecting a claim supported by a specific example in the specification. Here, there can be no dispute that disclosing the q4/q12 dosing regimen permits a skilled artisan to recognize that the inventors possessed the claimed q4/q12 dosing regimen. Accordingly, Petitioner has failed to meet its burden of demonstrating that at least one challenged claim is unpatentable for lack of written description.

2. None of Petitioner's Cases Involve a Specification That Actually Discloses the Claimed Species

Petitioner relies on cases where courts found the specification lacked sufficient "blazemarks" to direct the skilled artisan to the claimed invention because

it disclosed a genus. *See* Paper 2 at 65-70. For example, in *Ruschig*, the challenged claim recited a chemical compound. The specification, however, merely disclosed a broad genus that included the claimed compound along with "half a million" others.[24] *In re Ruschig*, 379 F.2d 990, 993 (CCPA 1967). The '345 priority applications, unlike the specification in *Ruschig*, actually disclosed the claimed q4/q12 dosing regimen as an "exemplary" embodiment.

Petitioner argues that the '345 Patent discloses a genus of tens of thousands of dosing regimens, but that is not correct.[25] The specification does not merely say

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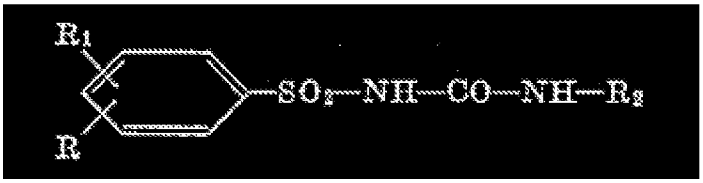
[24] The specification in *Ruschig* disclosed a genus that includes multiple unspecified substituents (R, R_1, R_2), as shown below, as opposed to a single compound:



[25] Petitioner misleadingly cites to a statement that Regeneron made during prosecution to argue that the '345 patent specification discloses a "virtually infinite" number of dosing regimens. Paper 2 at 68. During prosecution, to overcome a double patenting rejection, Regeneron explained that as of the filing date, the standard of care was monthly dosing but that there was a need in the art to extend that dosing and there were "virtually an infinite number of different treatment

the secondary dose must be between 2 and 4 weeks and the tertiary dose must be between 8 or more weeks. It provides specific examples which include q4/q12, as explained above.[26] Because the '345 patent discloses q4/q12 as an example, there is no need for "blazemarks." *UroPep*, 276 F. Supp. 3d at 656. To use Petitioner's analogy, the '345 Patent specification does not "disclose[] a forest" (Paper 2 at 66), it discloses many "tree[s]."

All of Petitioner's other cases are likewise inapplicable. *See, e.g.*, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) (finding patent invalid for lack of written description because there was no disclosure of the recited sub-genus, a

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protocols that could be tested." Ex. 1002 at 255. But, in making this statement, Regeneron was not talking about specific dosing regimens disclosed in the '345 specification, as Petitioner implies, but all dosing regimens that theoretically could be tested. *Infra* Section VII.C.3.

[26] Moreover, as Petitioner acknowledges, in addition to teaching that the secondary and tertiary doses can be administered at "different frequencies," the patent teaches they can be administered at the "same" frequency. Paper 2 at 67; Ex. 1001 at 4:23-34. In the latter case, where the timing of secondary and tertiary doses are fixed, the patent discloses only 70 examples: 5 exemplary secondary doses and 14 exemplary tertiary doses (5 x 14 = 70).

species within the sub-genus, or even a suggestion that the sub-genus was "of special interest"); *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367 (Fed. Cir. 2011) (same); *see also FWP IP ApS v. Biogen MA, Inc.*, 749 F. App'x 969, 975 (Fed. Cir. 2018) (finding claims invalid for lack of written description because specification did not teach that the recited dose could effectively treat multiple sclerosis, as recited by the limitation at issue); *Novozymes A/S v. DuPont Nutrition Bioscis. APS*, 723 F.3d 1336, 1348, 1341 (Fed. Cir. 2013) (finding claims directed to enzyme with particular properties invalid for lack of written description because there was no disclosure of a variant enzyme in the specification with all recited properties); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1327 (Fed. Cir. 2000) (finding written description not adequate where claims recited ratio of two pharmacokinetic parameters and nowhere was the recited ratio "discussed even in passing in the disclosure").[27]

[27] The *Uropep* court similarly distinguished many of the cases on which Petitioner relies. *UroPep*, 276 F. Supp. 3d at 655-656 (distinguishing *Novozymes*, *Boston Scientific*, *Fujikawa*, and *Ruschig*).

3. Petitioner's Argument Based on the Prosecution History Is Legally Irrelevant to Written Description and Factually Unsupported

Petitioner argues that (1) Regeneron took inconsistent positions during prosecution and (2) the '345 Patent claims lack written description for the same reason that Regeneron argued the 2009 Press Release did not anticipate during prosecution. Paper 2 at Sec. VIII.C. Neither argument has merit.

Regeneron's statements made during prosecution to overcome prior art are not legally relevant to the issue of whether the claimed dosing regimen is adequately supported by the '345 Patent specification. *Ariad*, 598 F.3d at 1351 ("the test [for written description] requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."). Petitioner cites no cases to support that proposition, nor does it even attempt to explain how they could be relevant. Paper 2 at Sec. VIII.B. This alone disposes of the issue.

Even if Regeneron's prosecution history statements were legally relevant, they are not inconsistent. During prosecution, the Examiner rejected the claims challenged by the Petition based on non-statutory double patenting. Ex. 1002 at 324-329. Regeneron argued that the pending claims to particular dosing regimens were nonobvious over some of the patents. *Id.* at 282-287. It argued that there was a need in the art to improve on the standard of care for wAMD by providing a method

requiring less frequent dosing than the prevailing fixed monthly dosing of ranibizumab. *Id.* at 283. Less frequent dosing would reduce the treatment burden of monthly intravitreal injections, including the expense, pain and inconvenience to the patient and physician. *Id.* Regeneron argued its less frequent dosing method was not *prima facie* obvious because there were "virtually an infinite number of different treatment protocols that could be tested." *Id.* Furthermore, even if the claimed invention were *prima facie* obvious, that finding would be overcome because the claimed invention exhibited unexpected results, as demonstrated by a 2012 paper by Heier *et al.* (Ex. 1012) ("Heier").[28] *Id.* at 284-285. Heier demonstrated that extended dosing of aflibercept (*i.e.*, less frequent than every month) "would be surprisingly as good or better than the results obtained with monthly treatment" [of prior art anti-VEGF therapies]. *Id.* at 285. The Examiner withdrew the obviousness-type double patenting rejection in view of Regeneron's unexpected results arguments. *Id.* at 225-226.

The Examiner later rejected the 12-week dosing claims as anticipated by the 2009 Press Release. According to the Examiner, the 2009 Press Release's disclosure of a "flexible PRN schedule" "would include at least one tertiary dose at 12 weeks from the immediately preceding dose." *Id.* Regeneron, however, explained that the

[28] Heier was published in 2012 and thus is not prior art to the '345 Patent claims.

2009 Press Release did not disclose the claim limitation "tertiary dosing administered 12 weeks after the immediately preceding dose." *Id.* at 210-211. The only reference to "12 weeks" in the Press Release was a reference "to a flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks"; the "[m]ere mention of a prospective possibility of dosing at 12 weeks does not explicitly indicate or teach towards a method where 12-week dosing would be undertaken, let alone successful." *Id.* at 176-177. The Examiner allowed the claims.

Petitioner argues that Regeneron took "inconsisten[t]" positions when it relied on "Heier (to overcome the first rejection) as sufficiently disclosing the claimed regimen to support unexpected results" and later critiqued "the 2009 Press Release as insufficient to disclose the same regimen" to overcome the second rejection. Paper 2 at 62. Petitioner's argument is wrong for several reasons.

Regeneron never argued that Heier "disclose[s] the claimed regimen." *Id.* Rather, Regeneron explained in prosecution that Heier supported the proposition that extended dosing regimens (such as those covered by the then-pending claims) were unexpectedly noninferior to the prevailing standard of care (*i.e.*, monthly injections of ranibizumab). *Supra*, p. 59. Moreover, even if Regeneron had argued that Heier disclosed the claimed regimen — contrary to the prosecution history — that would not have been inconsistent with Regeneron's statements regarding the 2009 Press

Release. Petitioner incorrectly asserts that the "2009 Press Release has essentially the same description as Heier." Paper 2 at 61. Petitioner ignores that Heier 2012 reports on the results of a clinical trial that had not been completed and were not known in 2009. By Heier 2012, both the frequency of dosing in the PRN regimen and the clinical trial results demonstrating efficacy were known, whereas at the time of the 2009 Press Release, neither of those things were known. Accordingly, there was nothing inconsistent in Regeneron's explanation that the Press Release failed to disclose 12-week dosing and that Heier demonstrated the success of extended dosing.

* * *

Petitioner's argument that the '345 Patent claims are invalid for lack of written description are not persuasive and Petitioner has not established that it is more likely than not that any claim challenged in Ground 3 will be found unpatentable.

VIII. CONCLUSION

For the reasons discussed *infra*, because Petitioner has failed to show: (1) that the '345 Patent claims are PGR-eligible; (2) that the Examiner materially erred in considering the same art or argument in prosecution; and (3) that any challenged claim is more likely than not unpatentable based on Grounds 1, 2, or 3, the Board should deny institution of the Petition.

Dated: April 15, 2021

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this preliminary response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This preliminary response contains 18,047 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

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

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§42.6(e)(4)(i) *et seq.* and 42.205(b), the undersigned Certifies that on April 15 2021, a true and entire copy of this **PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.**, and all supporting exhibits, were served via e-mail to the Petitioner at the following email addresses:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Patent No. 10,828,345

Post Grant Review No. PGR2021-00035

DECLARATION OF DAVID WU, M.D., PH.D

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Regeneron SEC Form 10-Q (May 4, 2007)	1030
Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)	1031
Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007).)	1032
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Exhibit Description	No.
U.S. Provisional Application 61/432,245	1045
U.S. Provisional Application 61/434,836	1046
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I. INTRODUCTION

1. I have been retained by counsel for Chengdu Kanghong Biotechnology Co., Ltd. ("Kanghong") as a technical expert in connection with the proceeding identified above. I have been asked to provide my opinions and views on the materials I have reviewed in relation to U.S. Patent No. 10,828,345 (the "'345 patent") (Ex. 1001) and the scientific and technical knowledge regarding the subject matter of the '345 patent before and at the earliest possible priority date. I submit this declaration in support of Kanghong's petition for post grant review of the '345 patent against Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron").

2. I am being paid at an 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. PROFESSIONAL BACKGROUND

3. I am the Joan Whitten Miller Scholar in Retina and an Assistant Professor of Ophthalmology at Harvard Medical School. In 2005, I completed my MD/PhD in the selective Inteflex program at the University of Michigan Medical School, followed by a residency (2006-09) in ophthalmology and medical retina/research fellowship (2009-10) at the University of Michigan Kellogg Eye

Center. I then pursued my vitreoretinal surgery fellowship at the Doheny Eye Institute / University of Southern California USC+LAC program. Afterward, I joined the faculty of the Massachusetts Eye and Ear Infirmary and Harvard Medical School (MEEI/HMS), serving until 2019 when I was recruited to the Wilmer Eye Institute at Johns Hopkins School of Medicine to serve in a similar capacity. In 2020, I was recruited back to MEEI/HMS as the Joan Whitten Miller Scholar in Retina.

4. I maintain an active medical and surgical retinal practice at the two major MEEI offices, in downtown Boston and in the Longwood Medical Area next to Harvard Medical School. I treat a variety of disorders including retinal detachments, macular holes, epiretinal membranes, age-related macular degeneration (AMD), retinal arterial and venous occlusions, and diabetic retinopathy. In my clinical practice, I frequently treat patients with VEGF antagonists, including Regeneron's aflibercept (Eylea), Genentech's ranibizumab (Lucentis), as well as off-label use of Genentech's bevacizumab (Avastin). Surgically, I have a particular interest in the repair of complex retinal detachments including those secondary to proliferative vitreoretinopathy and diabetic related traction. I have been named to Boston Magazine's honor roll of Top Doctors four times.

5. In addition to my practice, I run a research lab. My lab uses advanced techniques such as RNA-seq and AAV gene therapy in order to study the molecular mechanisms of retinal disease and develop new therapies. I most recently showed that selective overexpression of Nrf2 in the RPE of a mouse model of photoreceptor degeneration protected the RPE and preserved visual function. I am a co-inventor of the AAV vector to overexpress Nrf2 in the RPE, which is under consideration for clinical trials. I recently received a Thome Foundation grant to study the role of retinal metabolism and how it may factor in the development of early age-related macular degeneration. My research has been funded by the NIH/NEI, and I was the inaugural recipient of the MEEI Iraty Award for retinal diseases in 2017. To date, I have received over $1.25 million in funding for my research, with an additional $0.5 million pending.

6. I also teach ophthalmology. I have won several teaching awards throughout my career, and was named the Division Educational Champion for Retina resident education while on the faculty at the Johns Hopkins Wilmer Eye Institute. I am a faculty member of the MEEI/HMS vitreoretinal surgery fellowship program, and teach clinical management of retina problems and advanced vitreoretinal surgical techniques. My teaching includes local instruction on the management of medical and surgical retina conditions, including the

evaluation and management of medical retina disorders commonly treated by anti-VEGF agents such as wet AMD, diabetic retinopathy, BRVO, and CRVO. I have also lectured at regional and national continuing medical education events (CME) for Harvard Medical School and Johns Hopkins University. I have trained over 36 surgical and medical retina fellows who have gone on to careers in academic ophthalmology or private practice, as well as mentored several medical students and residents.

7. I am a member of the Association for Research in Vision and Ophthalmology, the American Academy of Ophthalmology, and the American Society of Retina Specialists; I am a diplomat of the American Board of Ophthalmology. I am a licensed physician in the states of Maryland, Massachusetts, and Michigan. I have served as an editor for the Journal of Visualized Experiments, JAMA Ophthalmology, American Journal of Ophthalmology, Ophthalmology, PLOS One, Investigative Ophthalmology & Visual Science, and Translational Vision Science and Technology. My research has been widely published; a full list of my publications can be found in my curriculum vitae (Ex. 1015).

III. BASIS FOR OPINION

8. My opinions and views set forth in this report are based on my education, training, and experience in ophthalmology, the materials I reviewed in preparing this report, and the scientific knowledge regarding the same subject matter that existed prior to the earliest filing of a patent application in the '345 patent family.

9. I have considered information from various sources in forming my opinions. Besides drawing on my experience as a clinician and researcher, I have reviewed the following materials: (a) the '345 patent (Ex. 1001), (b) the prosecution history of the '345 patent (Ex. 1002), (c) all prior art references cited herein including all prior art relied upon in my analysis of each challenged claim set forth below (including Ex. 1004-05), (d) all other documents and references cited herein (including Ex. 1006-47), and (e) the petition for post grant review of the '345 patent to which my declaration relates.

IV. SUMMARY OF MY OPINIONS

10. The '345 patent covers a dosing regimen of a VEGF trap comprising an initial dose, secondary doses every 4 weeks, and tertiary doses every 12 weeks. The '345 patent is anticipated by at least Shams, a Genentech patent application. Shams teaches the Regeneron's VEGF-Trap and the same dosing

regimen in claim 1 of the '345 patent, 4 week secondary dosing followed by 12 week tertiary dosing. Further, Shams explicitly teaches the additional limitations of dependent claims 2-11.

11. Claim 1 of the '345 patent is also obvious over Regeneron's own press releases published more than one year before the filing of the earliest patent application in the '345 patent family. In a 2009 press release about its clinical trials, Regeneron disclosed a dosing program that included 4-week secondary doses followed by 8 week tertiary doses. One of skill in the art would have found claim 1's dosing regimen obvious over the press release's dosing regimen, especially in view of Shams' 12-week tertiary doses. One or both of the 2009 Press Release and Shams teaches each limitation of the dependent claims of the '345 patent.

12. The '345 patent's claim 8 is not supported by a pre-2013 application. Claim 8 lists a number of diseases treatable by the 4 week plus 12 week dosing regimen, including Branch Retinal Vein Occlusion ("BRVO"). BRVO was not included in a pre-2013 application in the '345 patent family; the disorder was added in a July 2013 patent filing.

V. PATENT LAW STANDARDS

13. I am not an attorney. I have been informed about certain aspects of the law that are relevant to my opinions. My analysis and opinions are based on my expertise in this technical field, as well as the instructions for the legal standards relating to validity provided by counsel. My understanding of the law is as follows.

A. Claim Construction

14. I understand that before any invalidity analysis can be properly performed, the scope and meaning of the challenged claims must be determined by claim construction.

15. I understand that a patent may include two types of claims, independent claims and dependent claims. I understand that an independent claim stands alone and includes only the limitations it recites. I understand that a dependent claim depends from an independent claim or another dependent claim. I understand that a dependent claim includes all the limitations that it recites in addition to the limitations recited in the claim (or claims) from which it depends.

16. I understand that to determine how a person of ordinary skill would have understood a claim term, one should look to sources available at the time of the invention that show what a person of skill in the art would have

understood disputed claim language to mean. It is my understanding that this may include what is called "intrinsic" evidence as well as "extrinsic" evidence.

17. I understand that, in construing a claim term, one should primarily rely on intrinsic patent evidence, which includes the words of the claims themselves, the remainder of the patent specification, and the prosecution history. I understand that extrinsic evidence, which is evidence external to the patent and the prosecution history, may also be useful in interpreting patent claims when the intrinsic evidence itself is insufficient. I understand that extrinsic evidence may include dictionaries and other resources available to those of skill in the art at the time of the invention.

18. I understand that words or terms should be given their ordinary and accepted meaning unless it appears that the inventors were using them to mean something else or something more specific. I understand that to determine whether a term has special meaning, the claims, the patent specification, and the prosecution history are particularly important, and may show that the inventor gave a term a particular definition or intentionally disclaimed, disavowed, or surrendered claim scope.

19. I understand that the claims of a patent define the scope of the rights conferred by the patent. I understand that because the claims point out and

distinctly claim the subject matter, which the inventors regard as their invention, and claim construction analysis must begin with and is focused on the claim language itself. I understand that the context of the term within the claim as well as other claims of the patent can inform the meaning of a claim term. For example, because claim terms are normally used consistently throughout the patent, how a term is used in one claim can often inform the meaning of the same term in other claims. Differences among claims or claim terms can also be a useful guide in understanding the meaning of particular claim terms.

20. I understand that a claim term should be construed not only in the context of the particular claim in which the disputed term appears, but also in the context of the entire patent, including the entire specification. I understand that because the specification is a primary basis for construing the claims, a correct construction must align with the specification.

21. I understand that the prosecution history of the patent as well as art incorporated by reference or otherwise cited during the prosecution history are also highly relevant in construing claim terms. For instance, art cited by or incorporated by reference may indicate how the inventor and others of skill in the art at the time of the invention understood certain terms and concepts.

Additionally, the prosecution history may show that the inventors disclaimed or disavowed claim scope, or further explained the meaning of a claim term.

22. With regard to extrinsic evidence, I understand that all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises, can also be considered. For example, technical dictionaries may indicate how one of skill in the art used or understood the claim terms. However, I understand that extrinsic evidence is considered less reliable than intrinsic evidence, and for that reason is generally given less weight than intrinsic evidence.

23. I understand that in general, a term or phrase found in the introductory words or preamble of the claim, should be construed as a limitation if it recites essential structure or steps, or is necessary to give meaning to the claim. For instance, I understand preamble language may limit claim scope: (i) if dependence on a preamble phrase for antecedent basis indicates a reliance on both the preamble and claim body to define the claimed invention; (ii) if reference to the preamble is necessary to understand limitations or terms in the claim body; or (iii) if the preamble recites additional structure or steps that the specification identifies as important.

24. On the other hand, I understand that a preamble term or phrase is not limiting where a challenged claim defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention. I understand that to make this determination, one should review the entire patent to gain an understanding of what the inventors claim they invented and intended to encompass in the claims.

B. Anticipation

25. I understand that a challenged claim can be invalid for lacking novelty over the prior art, and that this concept is also known as "anticipation." I understand that a prior art reference anticipates a challenged claim, and thus renders it invalid by anticipation, if all elements of the challenged claim are disclosed in the prior art reference. I understand that the prior art reference does not have to use the same words as the challenged claim, but all of the requirements of the claim must be disclosed so that a person of ordinary skill in the art could make and use the claimed subject-matter.

26. I understand the disclosure in the prior art reference can be either explicit or inherent. I understand that a disclosure is inherent if it is necessarily present. I understand that inherency may not be established by possibilities or probabilities, and the mere fact that a certain thing may result is not sufficient. I

also understand that an inherent disclosure need not be recognized by those skilled in the art at the time of invention.

27. I understand that when a challenged claim covers several structures, either generically or as alternatives, the claim is deemed anticipated if any of the structures within the scope of the claim is found in the prior art reference.

28. I understand that when a challenged claim requires selection of an element from a list of alternatives, the prior art teaches the element if one of the alternatives is taught by the prior art.

29. I understand that a claimed range is anticipated by a prior art reference if the reference discloses a point within the range.

C. Obviousness

30. I understand that a claim is invalid if the differences between the claimed subject matter and the prior art are such that the claimed subject matter would have been obvious to a person of ordinary skill in the pertinent art at the time of the alleged invention.

31. I understand that obviousness must be determined with respect to the challenged claim as a whole.

32. I understand that one cannot rely on hindsight in deciding whether a claim is obvious.

33. I also understand that an obviousness analysis includes the consideration of factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the challenged claim, (3) the level of ordinary skill in the pertinent art, and (4) "secondary" or "objective" evidence of non-obviousness.

34. Secondary or objective evidence of non-obviousness includes evidence of: (1) a long felt but unmet need in the prior art that was satisfied by the claimed invention; (2) commercial success or the lack of commercial success of the claimed invention; (3) unexpected results achieved by the claimed invention; (4) praise of the claimed invention by others skilled in the art; (5) taking of licenses under the patent by others; (6) deliberate copying of the claimed invention; and (7) contemporaneous and independent invention by others. However, I understand that there must be a relationship between any secondary evidence of non-obviousness and the claimed invention.

35. I understand that a challenged claim can be invalid for obviousness over a combination of prior art references if a reason existed (at the time of the alleged invention) that would have prompted a person of ordinary skill

in the art to combine elements of the prior art in the manner required by the challenged claim. I understand that this requirement is also referred to as a "motivation to combine," "suggestion to combine," or "reason to combine," and that there are several rationales that meet this requirement.

36. I understand that the prior art references themselves may provide a motivation to combine, but other times simple common sense can link two or more prior art references. I further understand that obviousness analysis recognizes that market demand, rather than scientific literature, often drives innovation, and that a motivation to combine references may come from market forces.

37. I understand obviousness to include, for instance, scenarios where known techniques are simply applied to other devices, systems, or processes to improve them in an expected or known way. I also understand that practical and common-sense considerations should be applied in a proper obviousness analysis. For instance, familiar items may have obvious uses beyond their primary purposes.

38. I understand that the combination of familiar elements according to known methods is obvious when it yields predictable results. For instance, obviousness bars patentability of a predictable variation of a technique even if the technique originated in another field of endeavor. This is because design

incentives and other market forces can prompt variations of it, and predictable variations are not the product of innovation, but rather ordinary skill and common sense.

39. I understand that a particular combination may be obvious if it was obvious to try the combination. For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. This would result in something obvious because the result is the product not of innovation but of ordinary skill and common sense. However, I understand that it may not be obvious to try a combination when it involves unpredictable technologies.

40. It is further my understanding that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill in the art, not just the patentee. Accordingly, I understand that any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

41. Exemplary rationales that can support a conclusion of obviousness include:

- Combining prior art elements according to known methods to yield predictable results;
- Simple substitution of one known element for another to obtain predictable results;
- Use of known technique to improve similar devices (methods, or products) in the same way;
- Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- Choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to a person of ordinary skill in the art; and
- Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

42. A person of ordinary skill in the art looking to overcome a problem will often use the teachings of multiple publications together like pieces of a puzzle, even though the prior art does not necessarily fit perfectly together. Therefore, I understand that references for obviousness need not fit perfectly together like puzzle pieces. Instead, I understand that obviousness analysis takes into account inferences, creative steps, common sense, and practical logic and applications that a person of ordinary skill in the art would employ under the circumstances.

43. I understand that a claim can be obvious in light of a single reference, if the elements of the challenged claim that are not explicitly or inherently disclosed in the reference can be supplied by the common sense of one of skill in the art.

44. I understand that when the general conditions of a claim are disclosed, it is presumptively obvious to discover the optimum or workable ranges by routine experimentation. I understand that if the prior art recognizes that a variable affects a relevant property or result, then the discovery of an optimum value of the variable is obvious.

45. I understand that obviousness also bars the patentability of applying known or obvious design choices to the prior art. One cannot patent

merely substituting one prior art element for another if the substitution can be made with predictable results. Likewise, combining prior art techniques that are interoperable with respect to one another is generally obvious and not patentable.

46. In order for a claim to be found invalid based upon a modification or combination of the prior art, there must be reasonable expectation that a person of ordinary skill would have successfully modified or combined the prior art to arrive at the claimed arrangement. This does not mean that it must be certain that a person of ordinary skill would have been successful – the law only requires that the person of ordinary skill in the art would have perceived a reasonable expectation of success in modifying or combining the prior art to arrive at the claimed invention.

47. In sum, my understanding is that obviousness invalidates claims that merely recite combinations of, or obvious variations of, prior art teachings using understanding and knowledge of one of skill in the art at the time and motivated by the general problem facing the inventor at the time. Under this analysis, the prior art references themselves, or any need or problem known in the field of endeavor at the time of the invention, can provide a reason for combining the elements of or attempting obvious variations on prior art references in the claimed manner.

D. Written Description

48. I am informed and understand that the written description must actually or inherently disclose each and every element of a claim in order to meet the written description requirement. I am also informed that, to meet this requirement, a patent application must reasonably convey to those skilled in the art that the inventor had possession of the full scope of the invention. I am further informed that the words of the claim need not appear *in haec verba* in the written description but it is insufficient that undisclosed subject matter would have been obvious to a POSITA at the time the patent application was filed.

VI. BACKGROUND TECHNOLOGY

49. Many sight-threatening disorders of the eye are due to the dysfunction of blood vessels. Blood vessels perform the critical role of supplying oxygen and nutrients to all of our tissues, and so when their function becomes disrupted by disease, the consequences can be severe. This is particularly true in the eye, where the delicate nature, transparency, and compactness demanded of the visual apparatus to perform its function renders it extremely vulnerable to vascular dysfunction. One simplistic, but broad perspective is to classify clinically significant vascular dysfunction into two categories. The first category is neovascularization, in which new vessels grow into a part of a tissue where they

should not be, interfering with the function of and/or destroying the tissue into which it grows. The second category is loss of vascular integrity, in which the vessel walls become more leaky. As a result of vascular generation, there can be an escape of hematological components ranging from red blood cells to plasma components outside of the vascular lumens and into tissue that should remain "dry." This can be disruptive in the same way that it is destructive when water leaks into what should be a dry basement. Loss of integrity can also mean the insufficient transport of oxygen and nutrients, which in itself is detrimental to the health of the local tissue. In practice, these pathophysiological processes may overlap as vascular insufficiency can lead to neovascularization, and vessels borne of a neovascular process have less barrier integrity compared to healthy vessels.

50. Because pathophysiology of the vasculature is central to many eye conditions, it is an area that has been under intense study for many years. Through this work, it has become clear that the molecule, Vascular Endothelial Growth Factor (VEGF), plays a central role in this disease process as the key molecule mediating neovascularization and increase in vascular permeability. It is this recognition of the central role of VEGF as a promoter of angiogenesis (and cause of ocular disorders such as neovascular age-related macular degeneration) and the subsequent development of VEGF antagonists for clinical use that has

revolutionized the treatment of many eye conditions, allowing the restoration of sight in many patients who two decades ago would have been resigned to blindness.

51. The story of how anti-VEGF agents came into clinical use for the retina is fascinating, not just from a medical and scientific point of view, but also from a socioeconomic perspective. I also believe it to be relevant in understanding the evolution of the dosing regimen of these agents that most retina specialists now utilize. It is instructive to examine these revolutionary events through the perspective of wet age-related macular degeneration, the first ocular disease against which anti-VEGF agents were employed.

52. If one thinks of the eye as a camera, the retina is the film of the camera; and just as the film in a traditional camera, it resides along the back wall and is where the lenses focus the light that enters the eye/camera. The retina is a transparent, multi-laminar structure of cells, including the photoreceptor cells that convert light to biochemical and electrical signals that we perceive as vision. The central part of the retina, called the macula, has a particularly high concentration of cone photoreceptors - although it is small in surface area relative to the rest of the retina, it is critical because this high concentration of cones gives us the high

resolution vision that we take for granted as "sight" (such as the ability to read this document).

53. In many patients, the macula begins to degenerate with age (as one reaches the age of 50 and beyond), in a disease known as age-related macular degeneration (AMD). Approximately 11 million people in the US alone have some form of AMD, with the number projected to double by 2050 as modern medicine increases life expectancy. The degenerative changes typically begin with deposits of material forming under the retina in the absence of bleeding, which is a subtype of AMD known as "dry." Vision loss with dry macular degeneration can be slow, and in mild cases, of little clinical significance. However, in about 10% of these patients, the "dry" degenerative changes are supplanted by growth and dysfunction of blood vessels in the choroid. The choroid is a dense network of blood vessels residing just beneath the retina, whose function is to transport oxygen and nutrients to the photoreceptors. In some AMD patients, the choroidal vessels behind the macula undergo a neovascularization process, proliferating into a choroidal neovascular membrane (CNV) that subsequently leaks and bleeds. At this point, the patient is termed as converting to "wet" macular degeneration. This event can lead to abrupt vision loss, initially from the leakage of blood and fluid,

but then ultimately death of the photoreceptors, eventual central scarring and central blindness, and loss of one's high resolution vision.

54. As recently as the early 2000's, wet macular degeneration meant the severe and irreversible loss of functional vision. The only treatment that had shown any benefit up to that point was thermal laser, in which an ophthalmologist would apply a laser directly into the macula to target the CNV. While this would destroy the CNV, it would also cause scarring and an immediate central blind spot (scotoma) that was very noticeable to the patient. However, the idea was that the patients would eventually be worse off if they did not undergo this sight-robbing treatment – i.e., the treatment would prevent the later development of an even larger scar and scotoma had the CNV been allowed to continue to flourish on its own. This is well-described in the reports of the Macular Photocoagulation Study (MPS) which demonstrated the efficacy of this now outdated technique. The authors advised that "Both the ophthalmologist and the patient selected for treatment of subfoveal CNV should be prepared for an immediate decrease in visual acuity, 3 lines on average, with relatively stable visual acuity thereafter. No substantial treatment benefit was observed until 18 months after treatment, on average." (Ex. 1017.)

55. The next advance, photodynamic therapy (PDT), relied on the systemic infusion of a photosensitizing dye that preferentially accumulated in the CNV and whose toxic effects were then "activated" by application of a specific wavelength of light to the CNV itself in an attempt to limit the scope of the dye's toxicity. Like thermal laser, this treatment could still only slow the rate of vision loss in wet AMD patients. (Ex. 1018.) It is also worth mentioning that as limited as these treatments were, they worked best in only a subset of wet macular degeneration patients - those with a variant known as classic disease. Thus, for many years, the state of the art treatment for a wet AMD patient was to undergo examination and fluorescein angiography by a retina specialist. Those identified to have primarily classic disease were offered a treatment that might make things worse initially and would only slow their eventual vision loss; those without classic disease had even less hope. Needless to say, both retina specialists and patients were very eager to have a more effective treatment for this condition.

56. The anti-VEGF revolution for treatment of eye disease began in 2004. Thirty years after Dr. Judah Folkman at Harvard Medical School proposed the idea of specifically targeting an angiogenic factor to treat disease, Gragoudas, Adamis and colleagues published in the *New England Journal of Medicine* that intravitreal injections of Pegaptanib (Macugen), a ribonucleic acid aptamer that

selectively blocked one specific isoform of VEGF-A (VEGF165), could prevent vision loss. (Ex. 1019.) It was necessary to repeat the injection about every 6 weeks, and like PDT it was only able to slow the loss of vision. However, unlike PDT, it appeared to be effective regardless of the angiographic subtype of CNV.

57. Pegaptanib represents an important medical milestone in the application of anti-VEGF agents, but was quickly relegated to a historical footnote when the results of the phase 3 trial of ranibizumab were reported at the 2005 American Society of Retina Specialists (ASRS) meeting in Montreal, Canada. The results showed that Genentech's anti-VEGF agent, ranibizumab (Lucentis), administered by monthly intravitreal injections, actually *improved* the vision of patients with wet macular degeneration. Like pegaptanib, the treatment appeared effective against all subtypes of wet AMD rather than just primarily "classic." This marked the first time in history that retina specialists could tell their wet AMD patients that a treatment was available to actually make their vision better. Unlike pegaptanib, which selectively blocked one isoform of VEGF that was thought to be most important in eye disease, ranibizumab blocked all isoforms of VEGF-A. Studies soon showed that pegaptanib's theoretical safety advantage of blocking a specific isoform never materialized, and pan-VEGF-A blockade proved more effective, opening the door wider for anti-VEGF agents that block multiple

VEGF isoforms as well as other angiogenic molecules, including Regeneron's aflibercept (Eylea).

58. Not only was the 2005 ASRS meeting important for the presentation of the first clinical trial that improved vision in wet AMD patients, but it would also be remembered for the presentation of data regarding the off-label use of another anti-VEGF agent, bevacizumab (Avastin). Ironically also made by Genentech, bevacizumab had the same VEGF blocking domains as ranibizumab, but was a full length antibody. Bevacizumab had already been FDA-approved for intravenous administration to treat colorectal cancer as of 2004. Lucentis was still undergoing clinical trials at the time, but retina specialists were desperate for a more effective treatment. Phil Rosenfeld and colleagues at Bascom Palmer Eye Institute had recognized the similarities between bevacizumab and ranibizumab and had already begun to administer it to patients in an off-label manner. First, they systemically administered intravenous infusions of bevacizumab, showing wet AMD patients who received 2 to 3 intravenous infusions of bevacizumab over 6 months had equivalent results to those receiving monthly injections of ranibizumab. (Ex. 1020.) Secondly, they showed that an intravitreal injection of bevacizumab also resolved exudation from macular degeneration by OCT as seen

with ranibizumab, proof of concept that bevacizumab could be delivered in the same manner and with the same result as Ranibizumab. (Ex. 1019.)

59. The simultaneous reports created a unique situation. As previously described, ranibizumab, an anti-VEGF agent specifically developed for the eye, had demonstrated a paradigm shifting result (for the first time a treatment that improved the vision of wet AMD patients) in a landmark phase III clinical trial. Typically, one would have expected ranibizumab and the clinical trial's monthly dosing regimen to set the standard for treatment once FDA-approval was obtained. Yet, the success reported with the off-label use of bevacizumab, albeit in studies of much more limited scope, fundamentally changed the situation. Bevacizumab closely resembled ranibizumab on a molecular basis, was already available off-label, was manufactured by the same company, and was now reported to be effective when compounded for intravitreal injections. For so long there was no treatment for wet AMD, and now the promise of anti-VEGF to improve wet AMD patients was obvious with the ranibizumab results and available "today" if one was willing to use off-label bevacizumab. Thus, even before ranibizumab was FDA-approved for wet AMD in June 2006, retina specialists were already using bevacizumab off-label and improvising their own regimens based on their best clinical judgment.

60. One of the first reports on bevacizumab was presented at the AAO 2005 meeting in October 2005 and later published in the journal *Ophthalmology*. (Ex. 1022.) Although the anti-VEGF agent ranibizumab had been dosed at a 4 week interval for the clinical trials, the authors noted that for bevacizumab "The optimum dosing sequence for intravitreal bevacizumab is undetermined. We elected to defer reinjection into eyes when there was complete resolution of SRF, macular edema, and PEDs until there was a recurrence. Some patients have not recurred 15 weeks after a single injection." Not only did this report bolster the initial reports that bevacizumab was effective for wet AMD, but it also provided evidence that not all patients required monthly dosing and the rationale that dosing of anti-VEGF may be individualized.

61. This story illustrates that from the very beginning of the anti-VEGF revolution in the eye, retina specialists of ordinary skill and the art were already thinking of ways to test the durability of the treatment and extend the time between treatments. From the perspective of the retina specialist, as exciting as it was to suddenly have one, and maybe two treatments for a previously untreatable condition, the ground was shifting rapidly. Suddenly, patient outlook for wet AMD changed from having a blinding disease with poor treatment options to having a disease where vision could be restored with an injection. There was the

logistical challenge of accommodating a sudden change in practice pattern, in which a patient that previously would only need to be seen every 6-12 months for something that had little chance of improvement was now returning regularly, and potentially every month. There was concern our clinics would be overwhelmed with "injection patients." In addition, many of these patients were elderly and had difficulty getting to our offices in the first place - to ask them to come in every month would be stressful for them. Furthermore, there was great concern that these new treatments, while groundbreaking in terms of saving vision, could bankrupt the healthcare system. The wholesale cost of ranibizumab was $1950 per treatment, and one did not need to be an economist to understand the ramifications of potentially adding $1950 to the monthly health care bill of a million patients. All of these factors, as well as the early hints that bevacizumab (which cost about $100 per treatment) might have a similar effect over longer time periods, made it second nature to consider decreasing the frequency of anti-VEGF dosing in "real life." Consideration of these issues was not limited to retina specialists, as with the billions of dollars at stake, the esoterics of AMD treatment spilled over into the public eye (for example see Wall Street Journal "*Genentech's Big Drug for Eyes Faces a Rival*," (Ex. 1023)), and ultimately sparked the National Institutes of Health to embark on the Comparison of Age-related Macular Degeneration

Treatment Trials (CATT), comparing ranibizumab vs bevacizumab and monthly vs as-needed dosing.

62. For these reasons, there were intensive efforts on the part of the retina community to discover the true durability of anti-VEGF agents. Amongst the key studies during this time was the PrONTO study, which described the results of an as-needed (as also known as "*pro re nata*," or "PRN") regimen and established the central role of the OCT in determining the dosing requirements for a patient on anti-VEGF treatment. (Ex. 1024.) Although PRN dosing reduced the number of injections administered, the frequency of visits remained the same. Many retina specialists began adopting an alternative regimen, deemed treat-and-extend (TER). (Ex. 1025.) Essentially, this treatment strategy begins with regular fixed interval dosing, typically at the monthly interval, until the disease is under control. At that point, the intervals between exams and injections are extended, often by 1-2 week intervals. If the disease reactivates, the intervals between visits is then reduced to the previous successful interval with the goal of maintaining a fluid-free retina with the least number of office visits and injections as possible. Multiple surveys of the ASRS membership over the years suggest that TER remains by far the most popular regimen.

63. Recognizing these factors, the use of ranibizumab at extended intervals was studied. The PIER study explored quarterly (dosing every 12 weeks) administration following a series of three monthly injections. (Ex. 1026.) The study demonstrated quarterly dosing was superior to sham. However, the study populations in PIER were not directly compared to a monthly dosing regimen within the same study. A prospective study (EXCITE) directly compared monthly to quarterly dosing. This study was consistent with the findings in PIER in that both monthly and quarterly dosing of ranibizumab was able to improve vision of wet AMD patients, but that the vision of those dosed monthly improved to a greater extent. (Ex. 1027.)

64. Regeneron entered the VEGF antagonist arena in 2005, beginning within clinical development of VEGF Trap for treatment of AMD with a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study. The study included "a single dose of VEGF Trap-Eye at doses ranging of 0.05, 0.15, 0.5, 1, 2, and 4 milligrams (mg) intravitreally." (Regeneron SEC Form 8-K: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006) at 4-5 (Ex. 1028).) Based on the results, Regeneron initiated a Phase 2 trial in AMD. (*Id.*) The Phase 2 AMD clinical trial of intravitreally administered VEGF Trap (called "CLEAR-IT 2") included two groups receiving monthly doses of 0.5 or 2.0 mg of

VEGF Trap-Eye and three groups receiving quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). (Ex. 1013.) Thus, patients received an initial dose of VEGF Trap followed by either 3 secondary doses administered every 4 weeks until week 12, or one secondary dose administered at week 12. (*Id.*) In May 2007, Regeneron announced positive results of the trial, including for those patients dosed at 12 weeks only: "Moreover, patients in the dose groups that received only a single dose, on average, compared to baseline, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF Trap-Eye was generally well-tolerated." (Regeneron SEC Form 10-Q (May 4, 2007) (Ex. 1030) at 17-18; *see also* Regeneron SEC Form 8-K (Ex. 1031): "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007) at 24-25 (noting that monthly and quarterly dosing did not result in substantially different results at 8 weeks and that the results suggested the opportunity for a longer treatment interval using VEGF Trap-Eye).) An October 2007 Regeneron press release quoted Jeffrey Heier, M.D., a clinical ophthalmologist at Ophthalmic Consultants of Boston, a primary investigator in the Phase 2 study, and chair of the steering committee for the Phase 3 trial: "[the] results reaffirm the decision to study both the 0.5 mg and 2

mg monthly doses in the Phase 3 program . . . The quarterly dosing arms seemed to sustain their effect on visual acuity out to eight weeks, providing the rationale for exploring an eight-week dosing schedule in the Phase 3 program." (Regeneron SEC Form 8-K (Ex. 1032): "Press Release dated October 1, 2007" (October 1, 2007).) In an April 2008 press release announcing "Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration," Regeneron quoted Quan Dong Nguyen, M.D., M.Sc., Assistant Professor of Ophthalmology, Wilmer Ophthalmological Institute, the Johns Hopkins University School of Medicine, Baltimore, MD and a primary investigator in the Phase 2 study, as stating "it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly, especially on a chronic basis, without compromising visual acuity." (Regeneron "Press Release dated April 28, 2008" (Ex. 1033).)

65. On September 14, 2009 (the "2009 Press Release," Ex. 1005), Regeneron announced completion of patient enrollment in two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration. In the trials, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5 milligram (mg) every four

weeks, 2.0 mg every four weeks, or 2.0 mg every eight weeks (following three monthly doses), as compared with intravitreal ranibizumab administered 0.5 mg every four weeks during the first year of the studies. The 2009 Press Release also described two other trials, one a Phase 3 trial for treatment of central retinal vein occlusion ("CRVO") with six monthly doses of 2 mg VEGF Trap-Eye followed by PRN for another six months and the other a Phase 2 trial for treatment of diabetic macular edema ("DME") which included VEGF Trap-Eye dosed at 0.5 mg or 2.0 mg monthly, 2 mg on an as-needed basis after three monthly loading doses, or 2 mg every eight weeks after three monthly loading doses.

VII. THE '345 PATENT

66. The '345 patent has one independent claim, repeated below:

> 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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

67. Claim 1 has three sequential steps: (1) administer a single dose of a VEGF antagonist, (2) administer "secondary doses" of the VEGF antagonist every four weeks, and (3) administer "tertiary doses" of the VEGF antagonist every 12 weeks. The VEGF antagonist in the claimed dosing regimen is "a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component."

68. The dependent claims narrow independent claim 1 by specifying the drug administered (claim 2), modes of administration (claims 3 and 4), dose amount (claims 5-7), and the disorder(s) treated (claims 8-11). (Ex. 1001, Col. 22:56-23:13.)

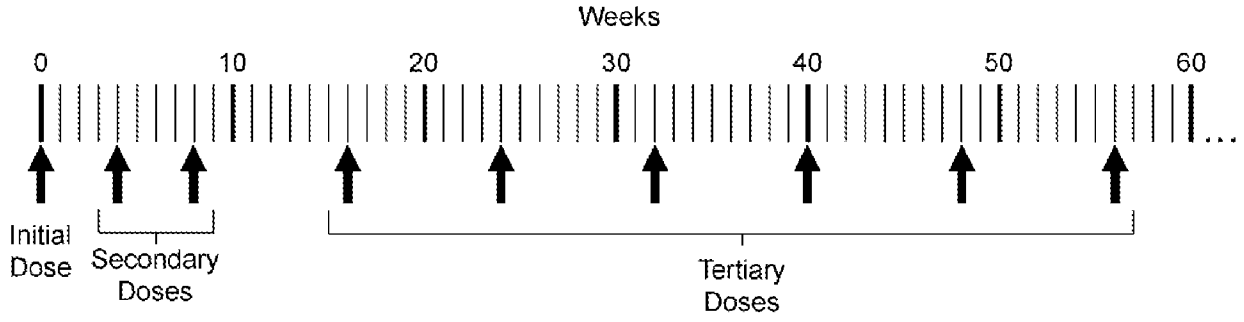
69. Claim 2 requires the VEGF antagonist to be aflibercept.

70. Claim 3 requires all doses are administered intraocularly and claim 4, which depends from claim 3, requires the doses are intravitreal.

71. Claim 5 requires all doses are within a range of 0.5 to 2.0 mg, claim 6 specifics 0.5 mg doses, and claim 7 specifies 2.0 mg.

72. Claim 8 requires the regimen treat one of a list of angiogenic eye disorders: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization. Claims 9-11 require one from the list: age related macular degeneration (claim 9), diabetic retinopathy, (claim 10), and diabetic macular edema (claim 11).

73. The '345 patent generally describes dosing regimens of monthly "secondary doses" followed by longer "tertiary doses." Figure 1 illustrates the dosing regimen with an 8-week tertiary dose.



74. The patent describes seven examples. Example 1 is "a Phase I study [where] 21 subjects with neovascular AMD received a single intravitreal (IVT) dose of VEGFT. Five groups of three subjects each received either 0.05, 0.15, 0.5, 2 or 4 mg of VEGFT, and a sixth group of six subjects received 1 mg."

(Ex. 1001, Column 8, Lines 4-27.) This example corresponds to Regeneron's Phase 1 trials described above.

75. Example 2 describes a Phase 2 clinical trial with "doses (0.5, 2, and 4 mg) of VEGFT tested at 4-week and/or 12-week dosing intervals. There were 5 treatment arms in this study, as follows: 1) 0.5 mg every 4 weeks, 2) 0.5 mg every 12 weeks, 3) 2 mg every 4 weeks, 4) 2 mg every 12 weeks and 5) 4 mg every 12 weeks." (Ex. 1001, Column 8, Lines 29-59.) This example corresponds to Regeneron's Phase 2 AMD trials, publicly announced in May 2007.

76. Example 3 describes a Phase 1 trial studying neovascular AMD, similar to Example 1. The subjects received 4 doses of VEGF-Trap over an eight-week period, with dose levels of 0.3, 1, or 3 mg per kg. (Ex. 1001, Column 8, Line 61 – Column 9, Line 20.) Example 3, like Examples 1 and 2, included no tertiary dosing.

77. Example 4 describes two Phase III clinical trials studying neovascular AMD. Patients were given one of the following dosing regimens: "(1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8); and (4) 0.5 mg ranibizumab administered

every 4 weeks (RQ4)." (Ex. 1001, Column 9, Line 22 – Column 14, Line 4.) This example corresponds to the Phase 3 AMD clinical trial described in the 2009 Press Release.

78. Example 5 describes a Phase 2 clinical trial in diabetic macular edema where "[t]wo groups received 0.5 or 2 mg of VEGFT once every four weeks throughout the 12-month dosing period (0.5Q4 and 2Q4, respectively). Two groups received three initial doses of 2 mg VEGFT once every four weeks (i.e., at baseline, and weeks 4 and 8), followed through week 52 by either once every 8 weeks dosing (2Q8) or as needed dosing with very strict repeat dosing criteria (PRN)." (Ex. 1001, Column 14, Lines 6–53.) This example corresponds to the DME trial described in the 2009 Press Release.

79. Example 6 describes a Phase 3 dosing study in CRVO where "patients received 6 monthly injections of . . . 2 mg intravitreal VEG Trap," then received 2 mg as needed. (Ex. 1001, Column 14, Line 55 – Column 15, Line 35.) This example corresponds to the CRVO trial described in the 2009 Press Release.

80. Example 7 lists 20 "examples of dosing regimens within the scope of the present invention." (Ex. 1001, Column 15, Line 36 – Column 17, Line 27.) Although Example 7 discloses tertiary dosing, the dosing frequency is described as either "once every 8 weeks," "less frequent" than the secondary dosing, or PRN.

None of the 20 exemplary dosing regimens provided in Example 7 include a 12-week tertiary dose as required by claim 1 of the '345 patent.

VIII. LEVEL OF SKILL IN THE ART

81. In determining the characteristics of a hypothetical person of ordinary skill in the art of the '345 patent at the time of the claimed invention, I considered several things, including various prior art techniques relating to treatment of angiogenic eye disorders, the type of problems that such techniques gave rise to, and the rapidity with which innovations were made. I also considered the sophistication of the technologies involved, and the educational background and experience of those actively working in the field at the time. I also considered the level of education that would be necessary to understand the '345 patent. Finally, I placed myself back in the relevant period of time and considered the doctors that I have worked with and educated in the field of retinal disease treatment.

82. I came to the conclusion that a person of ordinary skill in the field of art of the '345 patent would have been a person with a medical doctorate, an internship and residency in ophthalmology, and a 1-year medical retina fellowship or 2-year vitreoretinal surgical fellowship. A person with less education but more

relevant practical experience with retinal disease treatment may also be a person of ordinary skill in the art.

83. In the 2011-12 timeframe, a person of ordinary skill in the art would have known and had the skills necessary to administer intravitreal injections. An ophthalmologist with a 1-year medical retina or 2-year vitreoretinal surgical fellowship would have this experience. Since the introduction of bevacizumab and ranibizumab, general ophthalmologists also receive training in this area as part of their core residency and are familiar with the management of these conditions with intravitreal injections, but typically refer to retina specialists for treatment. Other knowledge and skills in 2011-12 included:

- Ability to examine a retina with dilated fundus examination,
- Ability to interpret fluorescein angiography,
- Ability to interpret optical coherence tomography, and
- Ability to perform intravitreal injections.

84. I would have qualified as a person of at least ordinary skill in the art as of the relevant timeframe. I have a sufficient level of knowledge, experience, and education to provide an expert opinion in the field of the '345 patent.

85. My opinions in this declaration are based on the perspective of a person of ordinary skill in the art as of the relevant timeframe.

IX. CLAIM CONSTRUCTION

86. To reach my opinions in this case, I have evaluated the claims of the '992 patent using my understanding of the patent law standards described above in Section V. I have given each word its ordinary and accepted meaning in the art. I have reviewed the claims, the patent specification, and the prosecution history and did not find that the inventors gave any claim term a meaning other than that commonly understood by a person of ordinary skill in the art.

X. ANALYSES OF CHALLENGED CLAIMS OF THE '992 PATENT

A. Shams discloses claims 1-11

87. Shams, published in 2006, was publicly available at least four years before Regeneron filed the earliest patent application in the '345 patent family. (Ex. 1004, Title Page.) Filed by Genentech in 2005, Sham's "Summary of Invention" describes treatment "methods includ[ing] administering to a mammal a number of first individual doses of a VEGF antagonist to the mammal followed by administering to the mammal a number of second individual doses of the VEGF antagonist." (Ex. 1004, Page 4, Line 31 – Page 5, Line 2.) Shams' Figure 2 illustrates an exemplary treatment plan using ranibizumab as the VEGF antagonist (Ex. 1004, Page 6, Lines 8-9):

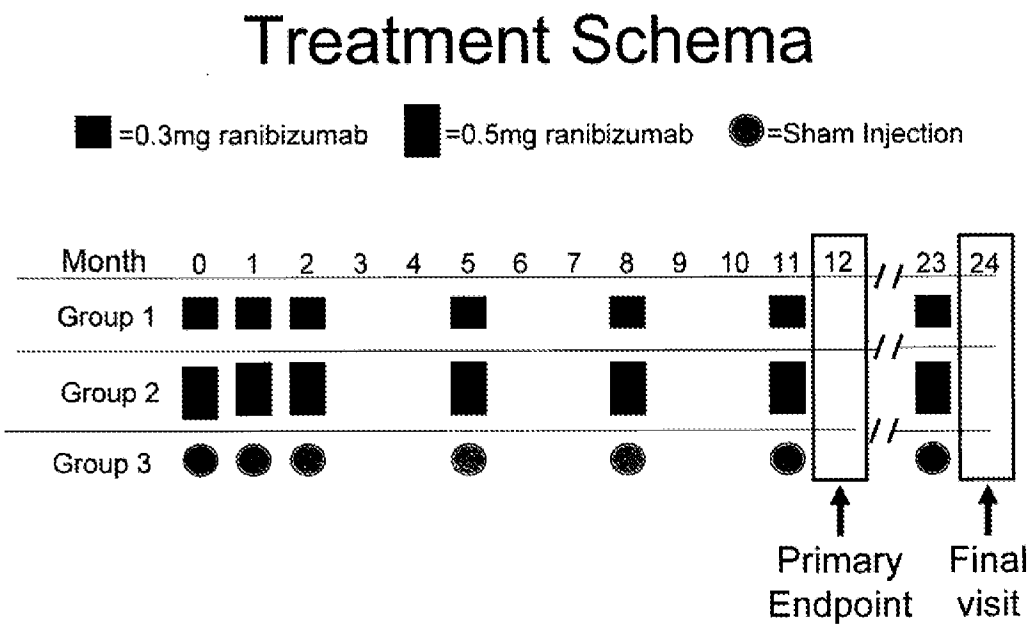


Figure 2

88. Shams discloses all the limitations of claim 1. Claim 1 covers a method for treating an angiogenic eye disorder in a patient; Shams discloses a method for treating "intraocular neovascular disease" in a "mammal." (Ex. 1004 at Page 4, Line 31 – Page 5, Line 2; *see also* Page 1, Lines 5-9.) One of skill in the art would understand "intraocular neovascular disease" to include the "angiogenic eye disorders" of claim 1. For example, the '345 patent's claims 8-11 list specific disorders (e.g., age-related macular degeneration) under the "angiogenic eye disorders" umbrella that Shams includes as examples of "intraocular neovascular diseases:"

> An "intraocular neovascular disease" is a disease characterized by ocular neovascularization. Examples of intraocular neovascular diseases include, but are not limited to, e.g., proliferative retinopathies, choroidal neovascularization (CNV), age-related macular degeneration (AMD), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, etc.

(Ex. 1004, Page 21, Lines 1-6; *see also* Shams "Background of Invention," Page 1, Lines 12-14 ("Angiogenesis is implicated in the pathogenesis of intraocular neovascular diseases, e.g., proliferative retinopathies, age-related macular degeneration (AMD), etc., as well as a variety of other disorders.").) Although Shams generally refers to treatment of "mammals," Shams includes "a patient" (as used in '345 patent, claim 1) within the treatment plan. For example, Shams describes a "therapeutic dose" as having "a therapeutic effect on the patient." (Ex. 1004, Page 20, Line 33; *see also* Shams Page 23, Lines 30-32 ("Another aspect of the invention is the treatment of an intraocular neovascular disease, e.g., wet form AMD, by administering to a mammal, preferably a human patient").) Thus, although Shams sometimes uses different language than the '345 patent, one of skill in the art would understand Shams to disclose claim 1's "method for treating an angiogenic eye disorder in a patient."

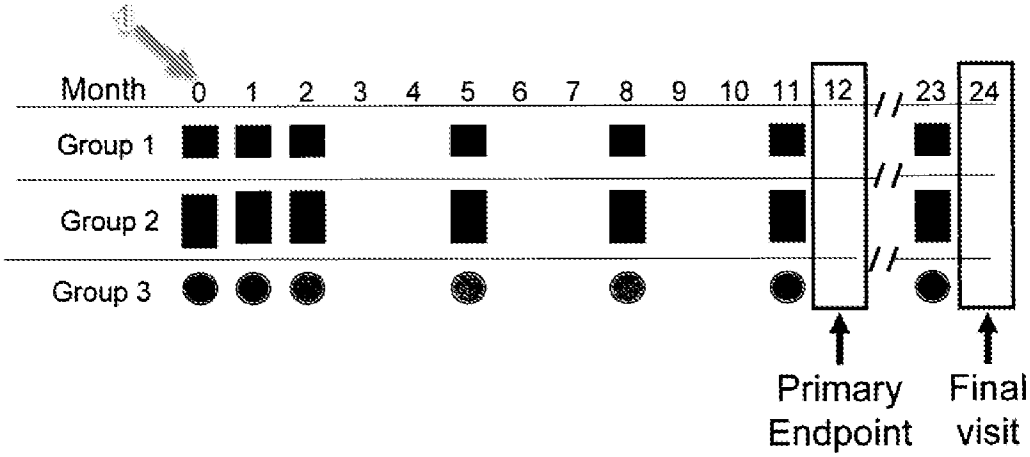
89. Claim 1 includes sequentially administering doses of a VEGF antagonist to the patient. As shown in Figure 2 above, Shams discloses administering the doses at different points in time, which is the definition of "sequentially administered" given in the '345 patent. (Ex. 1001, Column 3, Lines 32-36 ("'[S]equentially administering' means that each dose of VEGF antagonist is administered to the patient at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months).").) Claim 1 requires the VEGF antagonist to be "a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component." As is commonly known in the art, Regeneron's VEGF-Trap is such a molecule. (*See* Ex. 1001, col. 2, lines 41-45 ("In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a 'VEGF-Trap' or 'VEGFT'). An exemplary VEGF antagonist [is] 'VEGFR1R2-FcΔC1(a)' or 'aflibercept.'"); *see also* Ex. 1001, claim 2 (listing "aflibercept" as an example of the VEGF antagonist in claim 1).) Shams explicitly discloses Regeneron's VEGF trap:

> A "VEGF antagonist" refers to a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing or interfering with VEGF activities including its binding to one or more VEGF receptors. VEGF antagonists include anti-VEGF

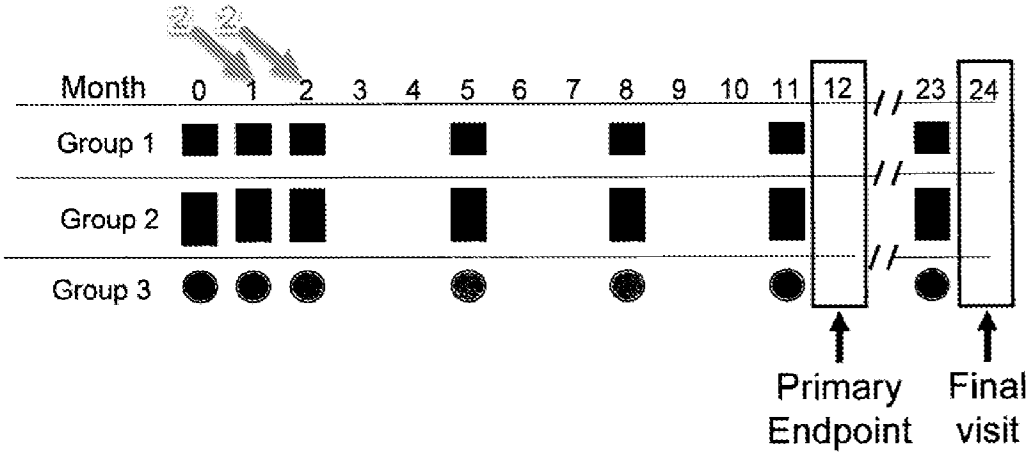
> antibodies and antigen-binding fragments thereof, receptor molecules and derivatives which bind specifically to VEGF thereby sequestering its binding to one or more receptors, anti-VEGF receptor antibodies and VEGF receptor antagonists such as small molecule inhibitors of the VEGFR tyrosine kinases, and fusions proteins, e.g., VEGF-Trap (Regeneron), VEGFi 2rgelonin (Peregrine). VEGF antagonists also include antagonist variants of VEGF, antisense molecules directed to VEGF, RNA aptamers specific to VEGF, and ribozymes against VEGF or VEGF receptors. Antagonists of VEGF act by interfering with the binding of VEGF to a cellular receptor, by incapacitating or killing cells which have been activated by VEGF, or by interfering with vascular endothelial cell activation after VEGF binding to a cellular receptor. All such points of intervention by a VEGF antagonist shall be considered equivalent for purposes of this invention.

(Ex. 1004, Page 6, Line 27 – Page 7, Line 6 (emphasis added).)

90. Claim 1's treatment plan includes a single initial dose of the VEGF antagonist. Shams discloses a single initial dose at "day 0" (labelled with numeral "1" below):



91. Claim 1's treatment plan continues with "secondary doses" administered 4 weeks after the immediately preceding dose. In my opinion, Shams discloses secondary doses every 4 weeks. For example, the second and third doses (labelled with numeral "2" below) in Shams' Figure 2 meet the claimed "secondary doses":



Shams does not use the term "secondary doses" for the second and third doses, instead grouping them with the initial dose as "first individual doses." (*See e.g.* Ex. 1004 at Page 5, Lines 20-21 ("In one embodiment of the invention, the first individual doses are administered at one month intervals (e.g., about 3 individual doses). Typically, there is more than one first individual dose.").) Although the '345 patent uses different language, Shams discloses the same "secondary doses." The '345 patent defines "initial dose" to be "the dose which is administered at the beginning of the treatment regimen" (Ex. 1001, Column 3, Lines 44-46); this is

Shams' "day 0" dose. The '345 patent defines "secondary doses" to be "the doses which are administered after the initial dose" (Ex. 1001, Column 3, Lines 46-47); in Shams, the doses at month 1 and month 2 follow the single initial dose at day 0. Thus, Shams' doses at month 1 and month 2 are the '345 patent's secondary doses.

92. It is my opinion that one of skill in the art would understand claim 1's "four week" dosing and Shams "one month" dosing to be the same dosing frequency. Typically, surgeons and patients calendar follow-up treatments on a weekly basis (i.e., the same day (and time) of a following week), instead of returning on the same date in a future month. In those cases, returning "monthly" is understood to mean returning in 4 weeks on the same day of the week. By contrast, surgeons and patients avoid reusing the same calendar date for return treatments because patients need to review their weekly schedules for conflicts and calendar date appointments fail when the date falls on a weekend. Additionally, many surgeons have practices in different locations. Typically, the surgeons visit a specific office location on the same day of every week. In such instances, the surgeon and patient may arrange a one-month "follow-up" but imply meeting on the same day in a future week. Further, monthly injections of Lucentis are well known, as pointed out in the '345 patent. This monthly interval is stipulated in part by the FDA-approved dosing guidelines for ranibizumab which state that the

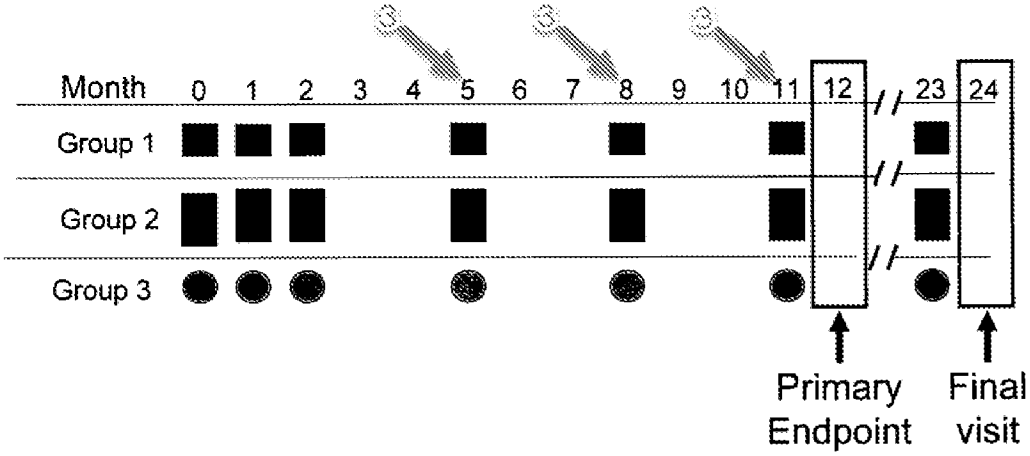
medicine should be administered between every 28 days and every 3 months. (FDA, Lucentis, Initial US Approval: 2006. US BLA (BL125156) Ranibizumab Injection (Ex. 1029).) With this justification, many Medicare Administrative Contractors do not cover lucentis more frequently than every 28 days per eye (For example, CMS, Local Coverage Determination (LCD) for Ranibizumab (Lucentis) (L29266, First Coast Service Options, Inc June 14, 2011 (Ex. 1034)). More frequent use of Lucentis was deemed a "questionable billing for medical ophthalmology services" in a report by the deputy inspector general for evaluation and inspections for HHS. (Ex. 1035.) Aflibercept is similarly not allowed more frequently than every 28 days based on its FDA approval, and a similar limit is placed on bevacizumab even though it does not have FDA guidelines for ophthalmologic use. (Ex. 1036.) In the rare circumstances that more frequent dosing is needed, a retinal specialist may alternate a more costly medicine such as ranibizumab or aflibercept that will be covered by insurance with bevacizumab, which the patient can afford to pay out of pocket.

93. The '345 patent supports my opinion. The '345 patent uses "four week" dosing and "monthly" dosing interchangeably. For example, the '345 patent describes a dosing frequency of "2 mg monthly (2Q4)." (Ex. 1001, Table 1, Column 13, Lines 29-32.) "Q4" is understood in the art to be shorthand for dosing

"every 4 weeks" (*see, e.g.*, Ex. 1001, Column 9, Lines 60-61.) Thus, the '345 patent treats "monthly" and "Q4" (i.e., every "4 weeks") as equivalent. Other disclosure in the '345 patent describes monthly as including "4 weeks." (*See, e.g.*, Col. 14:59-66 (describing the patients in Example 6 as receiving "6 monthly injections . . . once every four weeks"); Col. 15:40-41 (describing a dosing regimen of Example 7 as "once every 4 weeks (monthly)").) Shams too uses "monthly" broadly. For example, Shams describes the prior art methods as "administered in equal monthly (about 28 days) doses of 0.3 mg or 0.5 mg." (Ex. 1004, Page 24, Lines 2-4.)

94. Regeneron's own publications are consistent with my opinion. A 2011 Regeneron publication to Heier equated "4 week" with "monthly" dosing when describing the results of Regeneron's Phase 2 study: "During the 12-week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses." (*Heier et al*, "The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing," Ophthalmology ,Volume 118, Number 6, June 2011, (Ex. 1013) at 1110, Legend for Figure 2.)

95. Following the secondary doses, claim 1 requires "tertiary doses" administered every 12 weeks after the immediately preceding dose. Again, Shams discloses the claimed tertiary doses. In Shams, doses at month 5, 8, and 11 follow the "secondary" doses at months 1 and 2.



96. As with the "secondary" doses, Shams does not use the same terminology for claim 1's "tertiary" doses, but again there is no difference. The '345 patent defines "tertiary doses" to be "doses which are administered after the secondary doses." (Ex. 1001, Column 3, Lines 48-49.) Shams month 5, 8, and 11 doses are administered after Shams' "secondary doses" at months 1 and 2.

97. As I described above, one of skill in the art would consider "4 week dosing" and "monthly dosing" to be equivalent. In the same way, one of skill in the art would find "12 weeks" and "three-month dosing" to be equivalent. With 12 week dosing, one of skill in the art might also use the term "quarterly"

dosing, which is another term used in Shams to describe the "tertiary doses" in the treatment plan. (Ex. 1004, Page 23, Lines 9-11 ("For example, doses may be administered on a monthly schedule followed by subsequent quarterly or more dose schedule.").) All of these terms would be considered equivalent and used synonymously by those skilled in the art. For example, a 2011 Regeneron publication to Heier equated "12-week" with "quarterly" dosing when describing the results of Regeneron's Phase 2 study: "During the 12-week fixed dosing phase, patients . . . in the quarterly dosing groups received 0.5, 2, or 4 mg of VEGF Trap-Eye every 12 weeks on day 0 and at week 12 for a total of 2 doses." (Ex. 1013 at 1110, Legend for Figure 2.)

98. Thus, it is my opinion that Shams discloses all the limitations of claim 1.

99. Shams also discloses the limitations of claim 2. Claim 2 specifies that the VEGF antagonist is aflibercept, another name for Regeneron's VEGF Trap, i.e., the drug referenced in Shams as a VEGF antagonist. (*See, e.g.*, Ex. 1001, col. 2, lines 41-45 ("In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a 'VEGF-Trap' or 'VEGFT'). An exemplary VEGF antagonist [is] 'VEGFR1R2-FcΔC1(a)' or 'aflibercept.'").) The '345 patent confirms that Regeneron's VEGF

Trap for eye disorders is called "aflibercept." (*See, e.g.*, Ex. 1001, col. 2, lines 51-54 ("Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients with neovascular (wet) age-related macular degeneration.").) As noted, Shams discloses VEGF Trap (Regeneron), and also specifies that the VEGF antagonist is used for treating eye disorders (for example, Shams' Title, "Method for Treating Intraocular Neovascular Diseases"), confirming that Shams is disclosing Regeneron's VEGF Trap treatment for eye disorders.

100. Claim 3 requires "all doses of the VEGF antagonist are administered to the patient by intraocular administration," which is also taught by Shams. Intraocular administration is disclosed by Shams at Page 25, Lines 15-16: "[t]he therapeutic compound for treatment of an intraocular neovascular disease is typically administered by ocular, intraocular, and/or intravitreal injection." (*See also* Ex. 1004, Page 5, Lines 12-13 ("In one embodiment, the administration of the VEGF antagonist is ocular. In one aspect, the administration is intraocular. In another aspect, the administration is intravitreal.").) This disclosure also includes the limitations of the '345 patent's claim 4, i.e. that "the intraocular administration is intravitreal administration".

101. Shams discloses the '345 patent's claims 5, 6, and 7. Claim 5 requires "all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist" and claim 6 requires a specific dose, 0.5 mg, within claim 5's range. Shams discloses the specific 0.5 mg dose of claim 6 that lies within claims 5's range. (Ex. 1004, Figure 2; Page 31, Lines 58-11.) For claim 7, Shams does not discuss the 2.0 mg dose as a specific dose, but does disclose the range 0.1 mg to 20 mg (Ex. 1004, Page 24, Lines 18-20) which encompasses the 2.0 mg dose of claim 7, as well as the range of claim 5 and 0.5 mg dose of claim 6.

102. Claim 8 ("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") lists various eye disorders treated by the dosing frequency, which are further specified in claims 9 (age related macular degeneration), claim 10 (diabetic retinopathy), and claim 11 (diabetic macular edema). Shams discloses all of the specific disorders in claims 9-11: "age-related macular degeneration (AMD), diabetic and other ischemia-related retinopathies, diabetic macular edema." (Ex. 1004, Page 21, Lines 1-6.) Thus, Shams discloses each of claims 8-11.

B. The 2009 Press Release in view of Shams renders claims 1-11 obvious

103. The 2009 Press Release was published on September 14, 2009, more than one year before the filing of the first application in the '345 patent family. As modified by Shams, the 2009 Press Release renders obvious claims 1-11.

i. The 2009 Press Release in view of Shams renders obvious claim 1

a. The 2009 Press Release

104. Regeneron issued the 2009 Press Release to announce its completion of enrollment in clinical trials evaluating the effect of "VEGF Trap-Eye" on wet AMD, CRVO, and DME. (Ex. 1005 at Title ("Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)").) The wet AMD trial included scheduled doses of 0.5 milligram (mg) every four weeks, 2.0 mg every four weeks, or 2.0 mg every eight weeks (with one additional 2.0 mg dose at week four), as compared with intravitreal ranibizumab administered 0.5 mg every four weeks during the first year of the studies. (*Id.* at 1, First and Fourth Paragraphs.) After the first year, patients would continue to be followed and treated for another year on a flexible, criteria-based extended PRN regimen with a

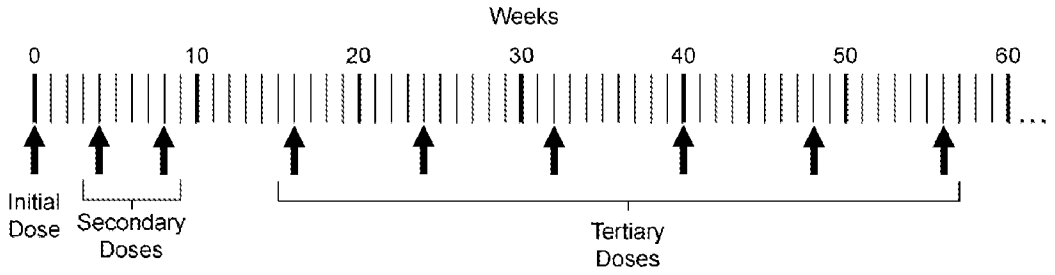
dose administered at least every 12 weeks, but not more often than every four weeks until the end of the study. (*Id.*) The 2009 Press Release also describes a "development for the treatment of [DME]" where VEGF Trap-Eye is dosed at 0.5 mg or 2.0 mg monthly, 2 mg on an as-needed basis after three monthly loading doses, or 2 mg every eight weeks after three monthly loading doses. (*Id.* at 2, Second Paragraph.)

b. The 2009 Press Release and Shams teach the limitations of claim 1

105. The 2009 Press Release teaches a method for treating an angiogenic eye disorder in a patient, as required by claim 1. For example, the trials included treatment of AMD and DME, both listed by the '345 patent as examples of angiogenic eye disorders. (*See, e.g.,* '345 patent dependent claims 8, 9, and 11.) The Press Release also teaches administration of the specific VEGF trap required by claim 1. The 2009 Press Release describes studies related to "VEGF Trap-Eye," which one of skill in the art would understand includes "a receptor-based chimeric molecule comprising an immunoglobin-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." (Ex. 1005 at 1, Last Paragraph ("VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PIGF)."); *Dixon*

et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," (2009) 18(10):1573-1580 (Ex. 1048).)

106. Claim 1 requires sequential administration of the VEGF antagonist, beginning with a single initial dose of the VEGF antagonist and followed by 4 week secondary doses. The 2009 Press Release describes two different trials that include 4 weeks doses followed by longer doses: (1) AMD treated with 2.0 mg doses "at an eight-week dosing interval following one additional 2.0 mg dose at week four;" (2) DME treated with "2 mg every eight weeks after three monthly loading doses." This is the same sequential dosing scheme as Figure 1 of the '345 patent.



107. The 2009 Press Release's first of the three monthly doses corresponds to the "initial dose" of the '345 patent's Figure 1 and claim 1. The second and third of the 2009 Press Release's three monthly doses correspond to the "secondary doses" of the '345 patent's Figure 1 and claim 1.

108. The 2009 Press Release treatment plan includes 8-week tertiary doses for both AMD and DME, and thus does not explicitly teach "each tertiary

dose is administered 12 weeks after the immediately preceding dose." Shams teaches 12 week tertiary doses. For example, Shams Figure 2 (reproduced below) schematically illustrates 4 week secondary doses and 12 week tertiary doses. I described Shams 12-week tertiary dosing above and incorporate that discussion here.

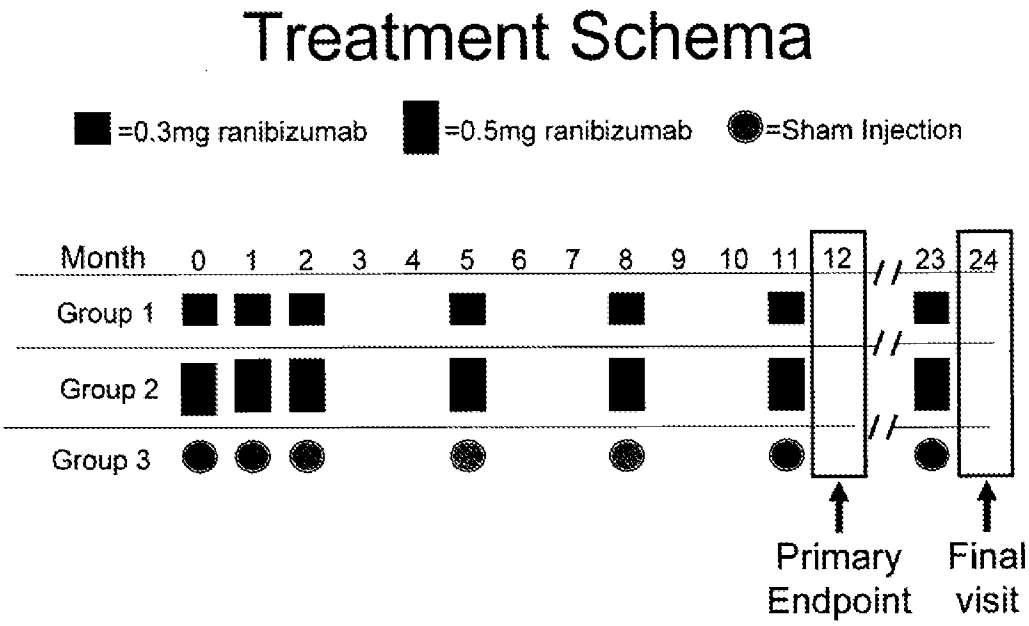


Figure 2

c. One skilled in the art would modify the 2009 Press Release's 4 + 8 treatment plans with Shams' 12 week tertiary dosing

109. By September 2009 (the date of the 2009 Press Release), the problems associated with monthly dosing VEGF antagonists were well known in the art. As I described earlier, VEGF antagonists revolutionized eye treatment

when first introduced. Before then, the treatment options involved preemptively causing partial blindness to avoid total blindness with laser, to later slowing down blindness with PDT or Pegaptanib. With VEGF antagonist treatments, patients now had a treatment choice that could potentially restore their vision.

110. After the initial excitement, those skilled in the art observed drawbacks with anti-VEGF treatments. As discussed earlier in this document, while VEGF antagonists were a significant advancement, the need for serial injections of a VEGF antagonist created many new burdens. One of these was mentioned in the 2009 Press Release, in which anti-VEGF treatments included "monthly office visits and examinations that are inconvenient for these often elderly patients." (Ex. 1005 at 1, Third Paragraph.) In my experience, the "inconvenience" in this article refers to the physical discomfort of receiving an intraocular injection as well as the mobility limitations of many elderly patients and their need to rely on others for help getting to and from the office. Cost is another drawback. In September 2009, a single injection of Lucentis costs almost $2,000 per month and so monthly injections cost $24,000 per year; any additional spacing of injections would reduce patient costs and would be very welcomed, given the high price of Lucentis. Again, retinal surgeons were also inconvenienced. With monthly injections, retina specialists' practice could consist

solely of providing maintenance injections to existing patients, giving few opportunities to expand a practice and treat new patients.

111. Given these market incentives, it was quite common in the art to dose VEGF antagonist at frequencies longer than monthly. This was termed "treat and extend" and, typically, included administering doses every 4 weeks initially, followed by less frequent doses. Contrary to the statements in the '345 patent, prior administration regimens for angiogenic eye disorders did not require monthly administrations throughout the entire course of treatment. (Ex. 1001, Column 2, Lines 26-30.) For example, Shams discloses non-monthly dosing, as I described above. Further, the FDA, in 2006, approved Lucentis for "treatment [of] one injection every three months after the first four injections if monthly injections are not feasible." (Ex. 1006 at 1.) Consistently, Regillo et al. reported, in 2008, that "Ranibizumab administered monthly for three months and then quarterly provided significant VA benefit to patients with AMD-related subfoveal CNV and was well tolerated. The incidence of serious ocular or nonocular adverse events was low." (Regillo et al., "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1," (Ex. 1026) at 1, Left Column, "Conclusions.")

112. With this backdrop, it was natural for one of skill in the art to consider extending the 2009 Press Release's 4 + 8 dosing regimens. Further, one of skill in the art would have looked to Shams when considering modifications to a VEGF antagonist dosing regimen for at least three reasons. First, Shams covers a dosing regimen for a Genentech VEGF antagonist. Genentech was an early leader in VEGF antagonist research and their research results are important to those skilled the art, especially around 2009-11. In 2009, Genentech offered one of the most popular VEGF antagonists on the market, Lucentis. Anyone considering VEGF antagonist dosing would look to Genentech's research of Lucentis (*see, e.g.*, Ex. 1001, Column 2, Lines 30-31 (citing "prescribing information for Lucentis® [ranibizumab], Genentech, Inc." when describing "prior administration regimens")). Shams reports on Genentech research on Lucentis and, thus, would be relevant to one of skill in the art working on Regeneron's dosing frequency. Second, Regeneron's clinical trials used ranibizumab to determine efficacy of its VEGF-Trap. For example, the 2009 Press Release states that the "primary endpoint of these non-inferiority studies" included comparison with "ranibizumab patients." (Ex. 1005 at 1, First, Fourth, and Fifth Paragraphs.) Given that Regeneron was comparing its drug's efficacy to ranibizumab in the 2009 Press Release, one of skill in the art would naturally look to Genentech's research of

ranibizumab—such as in Shams—to modify the 2009 Press Release's 4 + 8 dosing regimen. Third, Shams, in listing suitable VEGF antagonists for the 4 + 12 week dosing regimen, specifically identifies Regeneron's VEGF Trap.

113. One of skill in the art would modify the 2009 Press Release's 4 + 8 dosing regimen to 4 + 12 based on the teachings of Shams and on the 2009 Press Release teachings. First, Shams teaches that 4 + 12 dosing is possible. (*See, e.g.*, Ex. 1004, Page 23, Lines 9-11 ("For example, doses may be administered on a monthly schedule followed by subsequent quarterly or more dose schedule.").) Second, the 2009 Press Release teaches that 12-week tertiary dosing should be considered and is a potentially maximum length between tertiary doses. (Ex. 1005, ("During the second year of the study, . . . [tertiary doses] may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks.").) One of skill in the art would naturally consider 12 weeks as a desirable dosing regimen because both Shams and the 2009 Press Release explicitly teach a treatment plan with a 12-week dosing component.

114. One of skill in the art would have had a reasonable expectation of success when modifying the 2009 Press Release with Shams' 12-week tertiary dosing. For instance, Regeneron told its shareholders in 2007 that 12 week dosing works: "[P]atients in the dose groups that received only a single dose, on average,

compared to baseline, demonstrated a decrease in excess retinal thickness ($p < 0.0001$) and an increase in visual acuity ($p = 0.012$) at 12 weeks. There were no drug-related serious adverse events, and treatment with the VEGF Trap-Eye was generally well-tolerated." (Ex. 1031 at 24-25 (presenting analysis of the interim CLEAR-IT results as demonstrating that quarterly dosing (*i.e.*, dosing at week 0 and at week 12), on average, demonstrated an increase in visual acuity and a decrease in excess retinal thickness at both 8 weeks and 12 weeks into the study).) Further, Shams teaches that 12 week tertiary dosing of a VEGF antagonist is successful. As further evidence that 4-week followed by 12-week dosing would be successful, the FDA had previously approved ranibizumab for 4 + 12 dosing. (Ex. 1029; Ex. 1006.)

115. The modification of the 2009 Press Release's 8-week tertiary dose with Shams' 12-week tertiary dose would be routine to those skilled in the art. The modification merely combines prior art elements (Shams' 12-week tertiary dosing) with a known method (the 2009 Press Release's 4-week secondary dosing plus 8-week tertiary dosing) to arrive at a predictable result (a successful treatment of angiogenic eye disorders). Claim 1 is nothing more that the simple substitution of Shams' 12-week tertiary dose for the 2009 Press Release's 8-week tertiary dose.

ii. The 2009 Press Release in view of Shams renders obvious claims 2-11

116. Claim 2 specifies that the VEGF antagonist is "aflibercept." Aflibercept is another name for Regeneron's VEGF-Trap Eye. (Ex. 1001, Col. 2:38-41 ("An exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as 'VEGFR1R2-FcllCl(a)' or 'aflibercept.'").) Thus, the 2009 Press Release teaches "the VEGF antagonist is aflibercept."

117. The '345 patent specifies "intraocular administration" and "intravitreal administration" in claims 3 and 4, respectively. The 2009 Press Release teaches intravitreal administration: "VEGF Trap-Eye is being evaluated for its effect . . . when dosed as an intervitreal injection." (Ex. 1005 at 2, First Paragraph.)

118. Claim 5 requires that all doses of the VEGF antagonist are "from about 0.5 mg to about 2 mg" and claim 7 further narrows all doses to 2 mg. In the 2009 Press Release, the 4 + 8 AMD doses are administered at 2 mg and the 4 + 8 DME doses are also administered at 2 mg. (Ex. 1005 at 1, First Paragraph, and 2, Second Paragraph.) Thus, the 2009 Press Release teaches the specific dose of claim 7 and thus also teaches the range of claim 5. As described above, Shams

teaches the specific 0.5 mg dose of claim 6. Thus, the 2009 Press Release in view of Shams teaches each of claims 5, 6, and 7.

119. The '345 patent lists a number of angiogenic eye disorders in claim 8, including the specific eye disorders of claim 9 (AMD) and claim 11 (DME). The 2009 Press Release teaches treatment of both AMD and DME, teaching the specific eye disorders of claims 9 and 11 and, thus, also teach the elements of the list in claim 8. As described above, Shams teaches the eye disorders of claims 9-11. Thus, the 2009 Press Release in view of Shams teaches each of claims 8, 9, 10, and 11.

C. Claim 8 is not supported by an application filed before July 2013

120. Claim 8, which depends from claim 1, limits the angiogenic eye disorders treatable by the VEGF antagonist. The list includes age related macular degeneration ("AMD"), diabetic retinopathy, diabetic macular edema, central retinal vein occlusion ("CRVO"), branch retinal vein occlusion ("BRVO"), and corneal neovascularization. I understand that, to meet the "written description" requirement, a patent application must reasonably convey to those skilled in the art that the inventor had possession of each of these claimed disorders, including BRVO. It is my opinion that the pre-2013 applications in the '345 patent family do not convey that the inventor had possession of a method of treating BRVO.

121. When Regeneron filed the first application in 2011 and then the international application in 2012, the patent application listed "examples of angiogenic eye disorders that are treatable using the methods of the present invention," but the list did not include BRVO:

> The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include choroidal neovascularization, age-related macular degeneration (AMD), diabetic retinopathies, diabetic macular edema (DME), central retinal vein occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

(PCT Application No. PCTUS1220855, (Ex. 1016) Page 5, Paragraph 0025; *see also* U.S. Provisional Application 61/432,245, (Ex. 1045) Pages 5-6, Paragraph 0024; U.S. Provisional Application 61/434,836, Pages 5-6, Paragraph 0024 (Ex. 1046); U.S. Provisional Application 61/591,657, Pages 5-6, Paragraph 0024 (Ex. 1047).)

122. In the July 2013 filing, that paragraph was changed to list additional eye disorders "treatable using the methods of the present invention," including, for the first time, BRVO:

> The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye

> disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include age-related macular degeneration (e.g., wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; e.g., macular edema following CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; e.g., myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, and diabetic retinopathies.

(U.S. Application No. 13/940,370, (Ex. 1011) Page 5, Paragraph 0026 (emphasis added); *see also* Ex. 1001, Column 5:22-39.)

123. The table below compares the eye disorders included in the '345 patent prior to (left column) and after (right column) the July 2013 patent application. As show in the table below, no disorders were deleted from the paragraph, but the inventor more than doubled the listed disorders.

Pre-2013 Eye Disorders	**July 2013 Eye Disorders**
choroidal neovascularization, AMD, diabetic retinopathies, DME, CRVO, corneal neovascularization, retinal neovascularization	choroidal neovascularization, AMD, diabetic retinopathies, DME, CRVO, corneal neovascularization, retinal neovascularization,

	iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy, optic disc neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, retinal vein occlusion, BRVO

As can be seen in the table above, BRVO (along with a number of other disorders) was added to the '345 patent family in 2013. Thus, the pre-2013 patent applications did not list BRVO as one of the treatable eye disorders.

124. Nor is treatment of BRVO inherent in any of the disorders listed prior to July 2013. In 2012 (the time of the international filing) one of skill in the art would consider BRVO a different disorder than those listed prior to July 2013. One of skill in the art would not recognize a disclosed treatment of any of the pre-2013 disorders to be possession of a treatment for BRVO. In 2011-12, these were different indications, each with their own standard of care. One of skill in the art would not look at successful treatment of one ocular disease (e.g., choroidal neovascularization, AMD, diabetic retinopathies, DME, CRVO, corneal neovascularization, or retinal neovascularization) and understand that another ocular disorder (e.g., BRVO) is necessarily treated.

125. The paradigm-shifting success that anti-VEGF agents displayed with AMD made it obvious for retina specialists to consider the treatment of other vascular diseases, and the indications have risen over time. But this does not mean that a retina specialist would believe that successful treatment of one vascular disease necessarily followed from successful treatment of another. For example, cystoid macular edema (CME), which can be caused by a variety of disorders, presents similarly in an OCT image regardless of the cause. Despite the anatomical similarities, CME can respond differently to the VEGF Trap treatment, depending on the cause. We don't yet know why CME responds differently and sometimes the only way to distinguish between those underlying causes, given their anatomical similarities in an OCT image, is by testing the effects of anti-VEGF agents on a patient.

126. I would also like to provide a little more detail here regarding BRVO and CRVO, for which the pre-2013 application does disclose. Both involve impairments in the venous return system, but they are considered to be separate clinical entities for multiple reasons. Anatomically, BRVOs occur at a more distal part of the retinal venous tree, in which thickened, potentially atherosclerotic arteriole crosses a vein and impedes its flow. CRVOs occur when there is some obstruction on the other hand, occurring within the central retinal vein, and within

the optic nerve or up to the lamina cribosa, where the vein exits the nerve to enter the eye. Because of its much more proximal location in the venous tree, the damage from a CRVO is typically much more extensive and can involve the entire retina, whereas BRVO typically involves only a sector. Although there are overlapping risk factors for CRVO and BRVO, there are differences. For instance, Asians and Hispanics appeared to have an elevated risk of BRVO compared to Caucasians, whereas no similar difference was found for CRVO. (Ex. 1037.)

127. Aside from anatomical and population distinctions between BRVO and CRVO, another reason that one of skill in the art would not assume that a treatment of CRVO would be equivalent to be a treatment of BRVO is the historical difference in response to treatments between them. Prior to the anti-VEGF era, BRVO and CRVO were considered separately in landmark ophthalmology studies. Because of this, one would not have assumed that a treatment for BRVO would work for CRVO and vice versa. Two of the most important trials for vein occlusion treatment in the pre-anti VEGF era were the Branch Vein Occlusion Study (BVOS) and the Central Vein Occlusion Study (CVOS). Macular grid laser was found to improve cystoid macular edema (CME) and vision in BRVO patients and ultimately became the standard of care of its time (and is still used in some patients today). (Ex. 1038.) However, macular grid laser

was not found to improve vision in CRVO, and so the same treatment that was effective for BRVO was not recommended for CRVO. (Ex. 1039.)

128. The next series of landmark trials in BRVO and CRVO were the SCORE trials. BRVO and CRVO were again separated into distinct investigations. The conclusion of the SCORE BRVO trial was that there was no difference in visual outcome between standard of care to 1 mg or 4 mg triamcinolone, but the 4 mg triamcinolone arm had more side effects, so grid laser was still recommended. (Ex. 1040.) The conclusion of the SCORE CRVO trial was that triamcinolone at either dose improved visual acuity compared to standard of care, but that the 4 mg triamcinolone arm again had more side effects, making 1 mg triamcinolone a possible treatment option for CRVO. (Ex. 1041.) Thus, the SCORE CRVO and BRVO trials both considered the use of triamcinolone and reached different conclusions.

129. By this time, the VEGF antagonist ranibizumab was being tested for vein occlusions. Notably, there were separate trials performed for the study of ranibizumab's effects on BRVO and CRVO, supporting my opinion that one of skill in the art in 2011-2012 would not have assumed that treatments for one would necessarily work for the other. The BRAVO trial examined the efficacy of monthly ranibizumab for BRVO and the CRUISE trial examined the efficacy of

monthly ranibizumab for CRVO. Both trials found that monthly ranibizumab for 6 months followed by PRN treatment resulted in anatomical and visual improvement. (Ex. 1042, Ex. 1043.) These trials ultimately did demonstrate that both conditions benefited from anti-VEGF treatment, but given the historical differences in treatment for BRVO and CRVO one would not have assumed this to necessarily be the case. Furthermore, longer term follow-up of these cohorts found that while many patients with BRVO retained their visual acuity gains despite fewer injections in the second year, the treatment was less durable for CRVO, again supporting that these two conditions are different from a clinical standpoint. (Ex. 1044.)

130. My opinion is supported by the '345 patent and its history. First, claim 8 lists BRVO as a disorder separate from AMD, diabetic retinopathy, DME, CRVO, and corneal neovascularization. If treatment of these disorders implicitly included treatment of BRVO, there would be no need for the inventor to list BRVO as a separate treatment. Second, the '345 patent family added BRVO to the disclosed embodiments in 2013 along with other newly added disorders, confirming that the inventors recognized later that BRVO (along with the other disorders) was treatable with their VEGF antagonist.

131. Consistently, Regeneron structured their clinical trials differently for wet AMD, CRVO, and DME. In the 2009 Press Release, Regeneron reported (1) a Phase 3 clinical trial for wet AMD, (2) a Phase 2 clinical trial for CRVO, and (3) a Phase 2 clinical trial for DME. (Ex. 1005.) Each had different dosing regimens: (1) wet AMD was treated with scheduled doses of 0.5 milligram (mg) every four weeks, 2.0 mg every four weeks, or 2.0 mg every eight weeks (with one additional 2.0 mg dose at week four); (2) CRVO was treated with six monthly 2 mg doses, then on an as-needed basis; and (3) DME was treated with scheduled doses of 0.5 mg or 2.0 mg monthly, 2 mg on an as-needed basis after three monthly loading doses, or 2 mg every eight weeks after three monthly loading doses. The 2009 Press Release includes no mention of a BRVO clinical trial, much less a BRVO treatment plan with 4 week secondary doses and 12 week tertiary doses.

* * *

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

Dated: 1/7/21

David Wu, M.D., Ph.D

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner

Case PGR2021-00035
Patent 10,828,345

DECLARATION OF DIANA V. DO, M.D.

TABLE OF CONTENTS

I, Dr. Diana Do, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. ("Regeneron") as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials I have reviewed in relation to the Petition for Post Grant review of U.S. Patent No. 10,828,345 (the "'345 patent") (Ex. 1001), in particular the state of the art as of the earliest filing date ("priority date") of the '345 patent and responses to the opinion and views of Petitioner's declarant, David Wu, M.D., Ph.D. I submit this declaration in support of Regeneron's Patent Owner Preliminary Response ("POPR").

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

II. QUALIFICATIONS AND EXPERIENCE

3. I am a Professor of Ophthalmology and the Vice Chair for Clinical Affairs at the Byers Eye Institute at Stanford University School of Medicine and have been since 2017. I also serve as a Physician Improvement Leader at Byers Eye Institute, a position I have held since 2018. I have an active clinical and surgical practice and I work as a clinical investigator to study novel treatments for retinal diseases. In addition, I teach students, residents, and retina fellows at Stanford and am a member of the Stanford Ophthalmology Education Committee.

4. I graduated from the University of California Berkeley (summa cum laude) with a B.A. degree in Molecular and Cellular Biology in 1995 and earned my M.D. (Alpha Omega Alpha) from the University of California San Francisco School of Medicine in 1999. Following medical school, I completed an internship in internal medicine at Massachusetts General Hospital at Harvard Medical School. From 2000-2003, I completed my residency in Ophthalmology at the Wilmer Eye Institute at Johns Hopkins University School of Medicine, and then remained at the Wilmer Eye Institute for a Retina Fellowship in surgical and medical retina from 2003-2005.

5. From 2005 through 2010, I served as Assistant Professor of Ophthalmology and Assistant Head of the Retina Fellowship Training Program at the Wilmer Eye Institute. In 2011, I was promoted to Associate Professor and Head of the Retina Fellowship Training Program, positions I held through 2013.

6. In 2013, I joined the faculty at the Truhlsen Eye Institute at the University of Nebraska College of Medicine, where I became a full Professor of Ophthalmology in 2015. At the Truhlsen Eye Institute, I was Head of the Retina Fellowship Training Program and Program Director for the Ophthalmology Residency. In my leadership roles at the Truhlsen Eye Institute, I also served as Vice Chair of Education. I was recruited by Stanford University's Ophthalmology Department (the Byers Eye Institute) at Stanford in the beginning of 2017.

7. As a physician-scientist, I am an international leader in the treatment of diabetic retinopathy and wet AMD ("wAMD"). My research has led to more than 140 peer-reviewed publications. My research interest focuses on evaluating the efficacy and safety of novel pharmacologic therapies for diabetic macular edema, diabetic retinopathy, wAMD, retinal vein occlusion, and ocular inflammation. I have led national and global clinical trials investigating intravitreal VEGF inhibitors (aflibercept and ranibizumab) for diabetic eye disease and wet AMD. Our research developed a greater understanding of how intraocular inhibition of VEGF reduces vascular permeability and angiogenesis in diabetic eye disease, thereby reducing diabetic macular edema and improving visual acuity. Before the onset of pharmacologic therapies, thermal laser photocoagulation was the only treatment option for diabetic macular edema and laser was not effective in improving vision. Our research led to new treatment paradigms and better vision outcomes for patients with diabetic macular edema, diabetic retinopathy, and wAMD. The results from the collaborative research that I led has revolutionized how ophthalmologists throughout the world think about and treat patients with VEGF-mediated retinal diseases.

8. Since 2009, I have been the lead investigator and a Steering Committee member for the evaluation of aflibercept, a fusion protein that inhibits VEGF, in diabetic macular edema. I initiated the first-in-human clinical trial of aflibercept. In

addition, I also was the principal investigator on the Phase II and III clinical trials of aflibercept for diabetic macular edema to further evaluate efficacy, dosing regimens, and safety. My leadership in these global clinical trials, which enrolled over 1,000 subjects, contributed to FDA approval of aflibercept for diabetic macular edema. Aflibercept has also been approved by FDA for other angiogenic ocular diseases such as wAMD, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

9. My research efforts have also led to a greater understanding of the role of ranibizumab, an intravitreal VEGF antibody fragment biologic, in diabetic macular edema. I was a lead investigator in the Ranibizumab for Edema of the Macula in Diabetes (READ) Study Group and was the lead author on multiple manuscripts evaluating the efficacy and safety of ranibizumab. The collaborative studies that I led contributed to understanding dosing regimens for intravitreal VEGF inhibitors, and led to the design of pivotal clinical trials involving ranibizumab for diabetic macular edema. Ranibizumab was the first FDA approved intravitreal VEGF inhibitor for diabetic macular edema, and helped to transform the management of diabetic retinopathy. I continue to lead clinical trials investigating new treatments for retinal diseases.

10. As a result of my research, I am recognized as an international thought leader on the subject of the retina and am regularly invited to lecture and teach at

international and national meetings including the American Academy of Ophthalmology Retina Sub-Specialty Meeting, American Society of Retina Specialists, Asian Pacific Vitreo-Retinal Society Meeting, Canadian Ophthalmology Society Meeting, and congresses throughout Europe. I have organized and participated as a faculty member in national continuing medical education courses to teach my retina colleagues how to manage and treat diabetic macular edema, wet AMD, retinal vein occlusion, diabetic retinopathy, and other retinal disorders. Furthermore, I have held leadership positions at the American Society of Retina Specialists (Communications Committee Member to curate and develop online educational material), Women in Retina (Board Member and Secretary), Maryland Eye Society (President).

11. I am a practicing ophthalmologist with over 15 years of clinical and surgical practice in retina. I am a leader in the management of diabetic retinopathy, the leading cause of blindness in working age adults, and wAMD, the leading cause of vision loss in elderly individuals in developed countries. I have a high-volume clinical and surgical practice and spend approximately 1.5 days per week in clinic at the Byers Eye Institute and half-day per week at the Santa Clara Valley County Medical Center seeing patients in my clinical practice. In addition, I operate approximately one day per week at the Byers Eye Institute.

12. Given my extensive experience and research on diabetic retinopathy

and wAMD, I have become the expert retinal specialist and surgeon in our department for evaluating these chronic eye diseases. Since joining Stanford's Ophthalmology Department, I have also become one of the highest volume retina surgeons among our faculty. Because proliferative diabetic retinopathy can lead to tractional retinal detachment and bleeding within the eye, I am referred complex cases that often require clinic-based treatments (such as intravitreal injections of medicines or pan retinal laser photocoagulation) or surgical management. Since I have clinical and research expertise using intravitreal vascular endothelial growth factor (VEGF) inhibitors in wAMD, ophthalmologists refer patients to me for consultation or co-management, particularly of chronic cases that have not responded to therapy. The majority of my patients are from the Bay Area or central California, and approximately 10% travel from more than 5 hours away to seek my expert opinion. I have been recognized as a "Top Doctor" in the Bay Area for the past three years. A current copy of my curriculum vitae is included at Ex. 2022.

III. SUMMARY OF OPINIONS

13. My opinions and views set forth in this declaration are based on my education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '345 patent at the time of its earliest priority application.

14. In forming my opinions, I have reviewed the following materials: (a) the Petition for Post Grant Review of the '345 patent, PGR2021-00035, including all cited exhibits, (b) all priority applications leading to the issuance of the '345 patent, (c) all other documents and references herein, and (d) the Patent Owner's Preliminary Response to which my declaration relates.

15. For purposes of preparing this declaration in support of Patent Owner's Preliminary Response, I have been asked to apply Dr. Wu's definition of a person of ordinary skill in the art (who I also refer to as the "skilled artisan"): a person with a medical doctorate, internship and residency in ophthalmology and either a 1-year medical retina fellowship or a 2-year vitreoretinal surgical fellowship. Ex. 1003 ¶ 82. Likewise, for purposes of preparing this declaration, I have been informed and understand that the earliest filing date of the '345 Patent is January 13, 2011, based on the filing of a Provisional Application on that date.[1]

16. It is my opinion that by January of 2011, a person of ordinary skill in the art would have understood that branch retinal vein occlusion ("BRVO") was an "angiogenic eye disorder" that could be treated by a VEGF inhibitor. Likewise, it is my opinion that by January of 2011, the person of ordinary skill would have

[1] Although most of my opinions as to a skilled artisan expressed in this declaration are as of January 2011, I express some opinions as to the state of the art as of November 2011. In either case, I am applying the same definition of the skilled artisan.

understood that successful treatment of central retinal vein occlusion ("CRVO") with a VEGF inhibitor indicates that treatment of BRVO would also be successful.

17. It is also my opinion that by 2011, a skilled artisan would have understood that a fixed quarterly dosing regimen of ranibizumab, as disclosed in the Shams patent publication and corresponding PIER clinical trial, was a failure and not an effective method of treating an angiogenic eye disorder.

IV. THE '345 PATENT

A. Claim 1

18. The '345 patent has one independent claim, claim 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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

Ex. 1001 at 21:55-22:55

19. The dosing regimen of Claim 1 is directed to the treatment of any type of angiogenic eye disorder with a set of VEGF antagonist fusion proteins that

comprise an "immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is Fltl and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component."

20. The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at twelve week intervals following the preceding dose.

21. Claim 1 requires that "tertiary dose[s]" are "administered 12 weeks after the immediately preceding dose." Ex. 1001 at 21:59-64. As of the filing date, and even today, the term "tertiary dose" does not have a well-understood meaning to/ a skilled artisan in the fields of ophthalmology or retina medicine. In my experience, the term "tertiary dose" is not typically used by clinicians or the skilled artisan.

B. Claim 2

22. Dependent Claim 2 is directed to the method for treating angiogenic eye disorders with aflibercept, which is the unique fusion protein in Regeneron's Eylea product. Ex. 1001 at 22:56-57.

C. Claim 8

23. Dependent Claim 8 recites "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." Ex. 1001 at 23:3-8.

24. Claim 8 specifically lists types of eye disorders with pathological angiogenic characteristics, including several of the most significant "angiogenic eye disorders." A skilled artisan would recognize that these listed eye disorders are the major angiogenic eye disorders treated with VEGF antagonist pharmaceutical compounds.

25. The '345 Patent states that it is related to three provisional applications filed in 2011 — Provisional Application No. 61/432,245 (filed Jan. 13, 2011), Provisional Application No. 61/434,836 (filed Jan. 21, 2011), and Provisional Application No. 61/561,957 (filed Nov. 21, 2011). The January 13, 2011 Provisional Application, the earliest priority application, discloses methods that can be used to treat "any angiogenic eye disorder," which is defined as "any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage." Ex. 1045 at [0024]. The January 13, 2011 Provisional Application also provides non-limiting examples of angiogenic eye disorders including "choroidal neovascularization, age-related macular degeneration (AMO), diabetic retinopathies, diabetic macular edema (DME), central retinal vein occlusion (CRVO), corneal neovascularization, and retinal neovascularization." *Id.* The

provisional application also provides clinical trial data for Regeneron's aflibercept phase I, II, and III trials in wet AMD, and a phase II trial in DME. *Id.* at [0034]-[0041]. The November 21, 2011 Provisional Application adds the additional disclosure of clinical trial data for Regeneron's aflibercept phase III trial in CRVO. Ex. 1047 at [0064]-[0066].

V. STATE OF THE ART AS OF JANUARY 2011

A. Angiogenesis and VEGF Inhibition

26. Angiogenic eye disorders, also referred to as neovascular ocular diseases, are a group of diseases characterized by pathologic growth of abnormal blood vessels in the eye and vascular leakage from damaged, pre-existing blood vessels. Both events can lead to severe visual impairment. Angiogenesis is process controlled by a series of angiogenic agents such as growth factors, cytokines, and extracellular matrix components. One such agent is vascular endothelial growth factor ("VEGF"), a glycoprotein that acts as a potent proangiogenic factor. It has been well established that there is a correlation between elevated levels of VEGF and the presence of angiogenic eye disorders. Ex. 2004 at 23. Studies have demonstrated that elevated levels of VEGF are sufficient to induce ocular neovascularization and vascular leakage. *Id.*

27. VEGF plays multiple roles in the pathology of the angiogenesis in the retina. First, VEGF is a potent inducer of vascular permeability, which causes blood

vessels to leak and results in macular edema (swelling in the central retina) that causes vision impairment and is a common feature of angiogenic eye disorders. Ex. 2004 at 23. VEGF expression is upregulated by hypoxia (low oxygen in the tissue); hypoxia in the retina is commonly seen with retinal vascular diseases such as diabetic retinopathy, central retinal vein occlusion, and branch retinal vein occlusion where blood vessels in the retina are damaged and thereby fail to supply adequate oxygen to the retina. *Id.* Increased levels of VEGF in turn promote vascular permeability and angiogenesis, both of which threaten vision.

28. By January of 2011, a person of ordinary skill in the art recognized that a hallmark of angiogenic eye disorders was excess levels of VEGF in the eye. Correlations between elevated ocular levels of VEGF and presentation of ocular neovascular disease had been demonstrated in conditions such as iris neovascularization, retinal vein occlusion, diabetic retinopathy, diabetic macular edema, neovascular glaucoma, wAMD, and retinopathy of prematurity. Ex. 2004 at 23. The ordinarily skilled retinal specialist in 2011 understood that the term "angiogenic eye disorders" was a well-defined group of neovascular diseases. Indeed, there were no more than a few dozen types and subtypes of diseases that would be understood as comprising the universe of angiogenic eye disorder as of 2011. Ciulla and Rosenfeld illustrate in their 2009 publication in Current Opinion in Ophthalmology that there were nine distinct categories of neovascular eye

diseases, some of which exhibited neovascular characteristics that defined a subtype of that disease category. Ex. 2003 at Table 1.

29. By January of 2011, it was also well-established that inhibition of VEGF was a method for reducing this pathologic angiogenesis, and thereby treating the angiogenic eye diseases and improving vision prognosis. Ex. 2004 at 23. "The discovery of VEGF-A's role in the pathogenesis of neovascular ocular disease provided a strong rationale for the development of anti-VEGF-based therapies. There is now ample evidence that anti-VEGF therapies are viable treatment options for these [neovascular eye] diseases." Ex. 2003 at 1.

B. Methods of Treating Angiogenic Eye Disorders in the Art

30. Wet AMD is an angiogenic eye disorder characterized by abnormal growth of new blood vessels in the macula, the central portion of the retina responsible for high-resolution vision. Ex. 2025 at 2. Historically, wAMD was a devastating diagnosis that frequently led to irreversible vision loss. Early treatments with laser and photodynamic therapy would often, at best, slow inevitable vision loss. At worst, these treatments could cause further vision damage through retinal scarring. Wet AMD was the first angiogenic eye disorder where anti-VEGF agents were widely tested as a potential therapy. By 2006, however, two large Phase III clinical trials, MARINA and ANCHOR, demonstrated that intravitreal administration of an anti-VEGF antibody fragment, ranibizumab (or "Lucentis"), not

only slowed vision loss associated with wAMD, but could actually improve vision. Similar efficacy was likewise demonstrated by the use of another anti-VEGF antibody bevacizumab (or "Avastin") through off-label case studies. *E.g.*, Ex. 2024.

31. The MARINA trial ran from March of 2003 to December 2005 and enrolled 716 patients with AMD with either minimally classic or occult choroidal neovascularization. Ex. 2025 at 1. Patients were randomly assigned to received 24 monthly intravitreal injections of Lucentis (either 0.3 mg or 0.5 mg) or sham injections. *Id.* The primary endpoint of the study was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

32. The ANCHOR trial ran from May of 2003 to September of 2006 and enrolled 423 patients with predominantly classic choroidal neovascularization in wAMD. Ex. 2026 at 1. Patients were randomized on a 1:1:1 ratio 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 primary endpoint of the study was also the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

33. The two-year results of the MARINA trial were published in the New England Journal of Medicine on October 5, 2006. Ex. 2025 at 1. On the same day, the one-year results of the ANCHOR trial were also published in the New England Journal of Medicine. Ex. 2026 at 1. The two-year results of ANCHOR were

published in January 2009 in Ophthalmology. Ex. 2027 at 1.

34. The MARINA and ANCHOR trials demonstrated that monthly intravitreal Lucentis could not only effectively prevent vision loss, but could actually lead to mean improvements in vision that were sustained throughout the second year of the studies. In the MARINA trial, mean increases in visual acuity were +6.5 letters in the 0.3 mg group and +7.2 letters in the 0.5 mg groups, compared with a decrease of -10.3 letters in the sham-injection group. Ex. 2025 at 1. In fact, visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group. *Id.* Likewise, in the ANCHOR study, visual acuity was 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. 2026 at 1.

35. Lucentis received FDA approval for the treatment of wet AMD in June 2006. As demonstrated in its label, monthly injections of Lucentis resulted in sustained gains in visual acuity as compared to baseline vision. Ex. 2028 at 7. The successes seen in the treatment of wAMD with these anti-VEGF agents were a game-changer for the treatment of angiogenic eye disorders. As Ciulla and Rosenfeld noted in 2009, "[t]he success of anti-vascular endothelial growth factor (VEGF) therapies in neovascular age-related macular degeneration (AMD) has spurred investigation of similar treatment strategies for other exudative ocular diseases." Ex. 2003 at 1.

C. RVO, BRVO, and CRVO

36. Retinal vein occlusions ("RVO") was a recognized category of neovascular eye disease well-before January of 2011. Ex. 2004 at 23. CRVO and BRVO are closely related angiogenic eye disorders that were both known to fall within the category of RVOs. Ex. 2003 at Table 1 (RVO includes "Central RVO, hemicentral RVO, or branch RVO" based on the specific neovascular characteristics exhibited).

37. BRVO and CRVO share numerous disease characteristics including the development of a thrombus in the retinal vein resulting in reduced blood flow, dilation and tortuosity of the affected and damaged veins, retinal hemorrhages, cotton wool spots, evidence of ischemia, up-regulation of VEGF, and subsequent macular edema. If there is extensive ischemia in the retina, retinal neovascularization develops and can lead to vitreous hemorrhage and severe vision loss. Shared risk factors for RVOs include older age, arteriosclerosis, systemic arterial hypertension, and diabetes. Ex. 2029 at 1. The principal difference with these RVO subtypes is the locus of the occlusion. In CRVO, there is an obstruction of the retinal vein at or posterior to the optic nerve head, while in BRVO there is complete or partial obstruction at a branch or tributary of the central retinal vein.

38. As with other angiogenic eye disorders, the art recognized that anti-VEGF treatments could be a viable therapeutic option for patients with BRVO (and

CRVO) well-before 2011. As noted by clinicians at this time, "[h]igh levels of VEGF have been found in the aqueous humor of patients with ME [macular edema] secondary to vein occlusion. Accordingly, patients with higher levels of VEGF often have more severe cases of ME [macular edema]. Therefore, anti-VEGF therapy would seem a reasonable treatment option in these cases." Ex. 2006 at 2.

39. As early as 2005, researchers began testing the use of anti-VEGF agents, beginning with off-label intravitreal Avastin, on patients with BRVO and CRVO. Ex. 2029 at 1 ("Since the first report of the efficacy of intravitreal bevacizumab…in a patient with macular oedema secondary to CRVO in 2005, several retrospective case series have shown the benefit of this treatment, with an improvement in visual acuity and a decrease of central retinal thickness (CRT) in patients with macular oedema associated with both BRVO and CRVO.")

40. By 2009, studies "demonstrated rapid visual improvements after VEGF inhibition with ranibizumab and bevacizumab in patients with CRVO and BRVO." Ex. 2003 at 5. Despite being an off-label use, in 2009 the Patterns and Trends Survey by the American Society of Retina Specialists showed that approximately 50% of respondents used intravitreal Avastin as a first-line therapy for CRVO and BRVO. Ex. 2030 at 2.

41. By 2010, Genentech had completed full Phase III randomized controlled trials that assessed the efficacy and safety of intravitreal ranibizumab

(Lucentis®) in BRVO and CRVO. The BRAVO trial, which began recruitment in July 2007, evaluated ranibizumab injections compared with sham in patients with macular edema secondary to BRVO. In the BRAVO trial, 397 patients were randomly assigned to six monthly injections of ranibizumab, either 0.3 mg or 0.5 mg, or to sham injections. Ex. 1042 at 1. The primary efficacy outcome was mean change from baseline BCVA ("Best Corrected Visual Acuity") at 6 months. Secondary outcomes included the percentage of patients who gained 3 lines (15 letters) of BCVA at 6 months. *Id.* The mean visual acuity gain from baseline at month 6 was +16.6 letters in patients receiving 0.3 mg of ranibizumab, +18.3 letters in those receiving 0.5 mg, and +7.3 in those receiving sham injection. *Id.* at 2.

42. The CRUISE trial, which ran concurrently with the BRAVO trial and shared the same outcome measurements, evaluated ranibizumab injections compared with sham injections in patients with macular edema secondary to CRVO. Ex. 1043 at 1. The "results of CRUISE mirror those of BRAVO." Ex. 2030 at 2. In the CRUISE trial, 392 patients were randomized, the mean gain from baseline BCVA at month 6 was +12.7 letters in patients who received 0.3 mg ranibizumab, +14.9 letters in patients who received 0.5 mg ranibizumab, and +0.8 letters in those who received sham injections. Ex. 1043 at 1.

43. By June 2010, FDA had approved the use of Lucentis® (ranibizumab) on a monthly basis for the treatment of BRVO and CRVO. Ex. 2005 at 9.

VI. CLAIM 8 IS ADEQUATELY SUPPORTED IN THE ORIGINAL PROVISIONAL FILING

A. A Skilled Artisan Would Have Understood the January 13, 2011 Provisional Application's Disclosure of "Angiogenic Eye Disorders" to Include BRVO

44. The January 13, 2011 Provisional Application explicitly states that "[t]he methods of the present invention can be used to treat any angiogenic eye disorder, including, e.g., age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, corneal neovascularization, etc." Ex. 1045 at [0024]. The same application also defines "any angiogenic eye disorder," which is defined as "any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage." Ex. 1045 at [0024].

45. By January 2011, the set of "angiogenic eye disorders" was well-defined and, further, BRVO was widely recognized as an angiogenic eye disorder in that set. In addition, as discussed above, by January of 2011, BRVO had been successfully treated with anti-VEGF therapies, including bevacizumab and ranibizumab, which was widely reported in the literature. Further, before January of 2011, ranibizumab had been approved by FDA for treatment of BRVO by monthly intravitreal injection.

46. Given the known underlying pathology for angiogenic eye disorders and established efficacy of anti-VEGF agents in ameliorating that pathology, it is

my opinion that one of ordinary skill in the art, with Regeneron's January 13, 2011 Provisional Application in hand, would have understood it to be teaching that BRVO was a type of "angiogenic eye disorder," that could be treatable with a VEGF antagonist.

47. At paragraph 124 of his declaration, Dr. Wu suggests that in 2011-2012, one of ordinary skill in the art would not look at the successful treatment of one angiogenic ocular disease (e.g., choroidal neovascularization, AMD, diabetic retinopathies, DME, CRVO, corneal neovascularization, or retinal neovascularization) and understand that another ocular disorder (e.g., BRVO) could be treated.[2] Ex. 1003 ¶ 124. I disagree with Dr. Wu's assertion.

48. As noted above, by 2011, anti-VEGF agents had demonstrated efficacy with respect to many types of angiogenic eye disorders. Importantly, by 2011, anti-VEGF agents bevacizumab and ranibizumab (a VEGF antibody and a VEGF antibody fragment, respectively) had been shown to effectively treat BRVO. Indeed, Dr. Wu acknowledges that Genentech's BRAVO and CRUISE trials (Phase III trials of ranibizumab in BRVO and CRVO, respectively) demonstrated that both conditions benefit from anti-VEGF treatment. Ex. 1003 ¶ 129. The results of these

[2] While I have reviewed the entirety of Dr. Wu's declaration and there are many points on which he and I disagree, I do not attempt to respond or rebut each of these points of difference in this declaration. Rather, I reserve the right to respond more fully to Dr. Wu's declaration at a future date if asked to do so.

trials were presented in conferences around the world beginning in May of 2010. *See* Ex. 1042 at 9. In fact, in 2010, ranibizumab (Lucentis®) was FDA approved for "Macular Edema Following Retinal Vein Occlusion" without differentiating between BRVO or CRVO in the label. Ex. 2005 at 9. Given the successful experience in treating a variety angiogenic disorders, including BRVO and CRVO, with anti-VEGF agents before 2011, it is my opinion that a skilled artisan reading the January 13, 2011 Provisional Application, would have understood it to be teaching that "BRVO" was among the "angiogenic eye disorders" that could be treated with the disclosed treatment regimens.

49. In addition, at paragraph 125 of his declaration, Dr. Wu opines that a retina specialist would not think that anti-VEGF therapy could work for all vascular diseases, just because it worked for one such disease. In support of his assertion, Dr. Wu offers the example of the differential response of cystoid macular edema ("CME") to anti-VEGF treatment. Again, I disagree with Dr. Wu's statement and believe that his reliance on CME as a supporting example is misplaced. Dr. Wu ignores the fact that critical features of CME would directly, and predictably, impact the efficacy of an anti-VEGF agent on treatment of that disorder. Ex. 1003 ¶ 125. CME is a disease that has multiple etiologies; some, but not all, cases of CME are caused by angiogenesis. CME can also be caused by other factors, for example, inflammation after cataract surgery. Where CME is caused by inflammation after

cataract surgery, elevated levels of VEGF do not play a central role in the pathology as one sees in an ocular disorder that is characterized by angiogenesis specifically, and thereby inflammation-associated CME is usually treated with topical anti-inflammatory medicines. RVOs, including BRVO, by contrast, are normally associated with upregulated VEGF and, as a consequence, are susceptible to anti-VEGF therapy. Dr. Wu's CME example is thus a highly imperfect analogy to a skilled artisan's expectations with respect to BRVO.

B. A Skilled Artisan Would Have Understood the 2011 Provisional Applications To Teach that Regeneron's VEGF Antagonist Fusion Proteins Would Treat BRVO

50. The January 13, 2011 Provisional Application explicitly stated that one of the "angiogenic eye disorders" that could be treated by the disclosed methods was CRVO. This supports my opinion that a skilled artisan reviewing the provisional disclosures would have understood that an anti-VEGF agent would be an effective treatment for BRVO.

51. As noted above, BRVO and CRVO were known to be closely related types of RVOs that share numerous disease characteristics. As noted above, by January of 2011 it had become standard practice to treat both CRVO and BRVO with anti-VEGF agents and ranibizumab was tested in parallel Phase III trials in CRVO and BRVO. In fact, the retina community often described the results of BRAVO and CRUISE in tandem and did not distinguish between the subtypes when

announcing that anti-VEGF agents were effective for treatment of these closely related disorders. For example, David Brown, M.D., a clinical investigator on the studies noted that the trials "showed that with intensive, monthly treatment, patients achieve very good results, superior to anything we have seen previously with other treatment modalities." Ex. 2030 at 1. Other clinicians remarked of BRAVO and CRUISE "[t]hus far, off-label use of anti-VEGF drugs has been shown to effectively target the underlying pathogenesis associated with the development of ME secondary to vein occlusion." Ex. 2006 at 2.

52. Given the successful outcomes of these Lucentis Phase III trials for both BRVO and CRVO, an ordinarily skilled artisan would have understood that positive clinical trial results seen with one anti-VEGF agent in CRVO could forecast successful outcomes in a BRVO patient with that same anti-VEGF agent.

53. An ordinarily skilled artisan with the benefit of Regeneron's January 13, 2011 Provisional Application would have understood that aflibercept, a VEGF antagonist fusion protein, had demonstrated efficacy in two Phase III pivotal trials in wAMD. The January 13, 2011 Provisional Application describes these Phase III studies (in Example 4) and reports clinical trial results at the primary endpoint of 52 weeks. Ex. 1045 at [0038]-[0060]. The Phase III clinical results show that by week 52 in Study 1, the patients receiving aflibercept 2 mg every four weeks gained +10.9 letters and patients dosed every eight weeks gained +7.9 letters. *Id.* at [0038].

Similarly, in Study 2, patients who received aflibercept 2 mg every four weeks gained +7.6 letters and patients dosed every eight weeks gained +8.9 letters. *Id.*

54. In addition, Regeneron's January 13, 2011 Provisional Application disclosed that aflibercept was effective in a Phase II trial in DME. Ex. 1045 at [0061]-[0063]. Clinical trial results were reported at 24 weeks and 52 weeks. The Phase II results show that by week 52, patients who received aflibercept 2 mg every four weeks gained + 13.1 letters. *Id.* at [0061]. Likewise, patient who received aflibercept 2 mg every eight weeks gained +9.7 letters. *Id.*

55. Furthermore, Regeneron's November 21, 2011 Provisional Application disclosed clinical trial results from the COPERNICUS trial for the treatment of CRVO with aflibercept. Ex. 1047 at [0064]-[0066]. The COPERNICUS trial was a randomized, double-masked, phase III study where patients received 6 monthly injections of either 2 mg intravitreal aflibercept or sham injections. From week 24 to week 52 of the study, all patients received 2 mg aflibercept on a PRN (as-needed) basis according to pre-defined retreatment criteria. *Id.* at [0064]. The primary endpoint for the trial was the proportion of patients who gained $\geq$ 15 letters from baseline at week 24. The November 21, 2011 Provisional Application disclosed that at week 24, 56.1% of patients treated with aflibercept gained $\geq$ 15 letters as compared to 12.3% of sham treated patients. *Id.* at [0065]. And, at week 52, 55.3% of patients treated with aflibercept gained $\geq$ 15 letters as

compared to 30.1% of sham treated patients; the aflibercept arm gained a mean of +16.2 letters vs. +3.8 letters for sham patients. *Id.* This disclosure clearly demonstrated to a skilled artisan that 2 mg intravitreal aflibercept produced statistically significant improvements in visual acuity that were maintained through week 52 on the PRN dosing regimen.

56. Given the positive results reported in Regeneron's 2011 Provisional Applications regarding clinical trials with aflibercept in wAMD and DME, a person of ordinary skill in the art would have viewed the disclosure of COPERNICUS results in CRVO as a clear signal that Regeneron's anti-VEGF fusion protein therapy would be successful in treating BRVO.

57. At paragraphs 126-127 of his declaration, Dr. Wu opines that given known differences in the anatomy, affected patient population, and historical treatment differences between BRVO and CRVO, a person of ordinary skill in the art would not have assumed that a treatment for CRVO would equate to a treatment of BRVO. Ex. 1003 ¶126-127.

58. I disagree. Notably, Dr. Wu relies on historical differences in response to treatment "[p]rior to the anti-VEGF era" (Ex. 1003 ¶127) but by 2011, those historical differences were no longer relevant.

59. For example, at paragraphs 127-28, Dr. Wu discusses the disparate impact of macular grid laser treatment, a historical treatment modality, on BRVO as

compared to CRVO. Ex. 1003 ¶¶ 127-28. More specifically, macular grid laser treatment was found to improve vision for BRVO patients but not CRVO patients. However, Dr. Wu neglects to include important context about the nature of the diseases and how it relates to the particular treatment. As noted earlier, the key difference between BRVO and CRVO is the locus of the retinal vein occlusion. When using laser therapy treatment, this anatomic difference is highly relevant. BRVO responded better to laser treatment because the area of the vein occlusion is smaller, and a clinician can more easily target the specific retinal area that needs treatment. On the other hand, CRVO is posterior to the optic nerve and the diseased area is more extensive—it is impacting all four retinal quadrants – and macular laser is not effective in CRVO. These anatomic impacts on the efficacy of laser therapy have no relevance to the efficacy of anti-VEGF treatment, which seeks to arrest the cause of the vascular leakage and neovascularization in the first place by inhibiting the VEGF pathway.

60. By 2011, anti-VEGF therapy had been demonstrated to be effective for the treatment of BRVO and CRVO. In fact, Genentech's Lucentis® (ranibizumab) had been FDA-approved for the treatment of BRVO and CRVO by June of 2010. Ex. 2005 at 9. Thus, Dr. Wu's hypothetical concerns regarding differences in anatomy and historical treatment modalities for BRVO and CRVO (Ex. 1003 ¶¶126-127) were mooted once VEGF inhibition was demonstrated to be effective for

treatment of BRVO. Notably, Dr. Wu fails to acknowledge the critical role that Avastin had played in clinical practice for both of these RVO subtypes well before the 2011-2012 time frame during which he asserts that a skilled artisan "would not have assumed" that "both conditions could benefit from anti-VEGF." Ex. 1003 ¶ 129.

61. Dr. Wu also tries to differentiate BRVO and CRVO by noting that patient populations of different ethnicities have disparate risks for BRVO, but not for CRVO. Ex. 1003 ¶ 126. This is again a difference without a distinction. By 2011, anti-VEGF therapy had been shown to be effective in large, randomized Phase III clinical trials and there were no proven studies in 2011 (nor are there as of the present day) that show a disparate response to anti-VEGF therapy in patient populations of different ethnicities for either CRVO or BRVO.

62. Simply put, given the closely related nature of CRVO and BRVO and the demonstrated efficacy of anti-VEGF agents in treating both conditions by January 2011, it is my opinion that the disclosure of CRVO in the January 13, 2011 Provisional Application would have bolstered a skilled artisan's understanding that BRVO was an angiogenic eye disorder treatable by the disclosed methods of the '345 Patent.

VII. SHAMS DISCLOSED AN UNSUCCESSFUL 12-WEEK DOSING REGIMEN

63. I understand that Petitioner has asserted that the dosing regimen of

Claim 1 of the '345 Patent is not novel in light of Shams (Ex. 1004), a Genentech patent application that was published on May 4, 2006. I have reviewed Shams' disclosure and recognize that the Trial Design (Figure 1) and Treatment Schema (Figure 2) set forth in Shams, as well as its description of a dosing regimen in Example 1, all correspond to Genentech's PIER Study, a clinical trial of ranibizumab (Lucentis®). *Compare* Ex. 1004, Figure 2, *with* Ex. 1026 at 2.

64. The PIER study, which ran from August 2004 to March 2007, was designed to compare three monthly loading doses followed by fixed quarterly dosing of 0.3 mg and 0.5 mg Lucentis® (ranibizumab) against sham control over 24 months. Ex. 1026. at 2. This same dosing regimen is outlined in Figure 2 of Shams, which illustrates the administration of the "first individual doses" at months 0, 1, and 2, followed by the "secondary doses" at months 5, 8, 11, and continuing every 3 months through 24 months. Ex. 1004, Figure 2.

65. During the first year of the PIER Study, while the treatment arms gained visual acuity during the three monthly loading doses, those visual acuity gains were lost when patients transitioned into the quarterly fixed dosing period of the treatment regimen. Ex. 1026, Figure 1. Worse yet, by the end of month 12, both treatment arms had on average lost letters as compared to baseline. *Id.* In addition to the visual acuity losses reported in PIER, *post-hoc* analyses of the study data showed that patients in the treatment arm of PIER saw no benefit in the incidence of macular

hemorrhage as compared to sham control and, in fact incidence rates were numerically higher. Ex. 2020 at 3, 7. By the time PIER year one results were first presented, in September of 2006, Genentech had run two phase III ranibizumab trials —MARINA and ANCHOR — that demonstrated the efficacy of monthly intravitreal injections of Lucentis. Both clinical trials showed that Lucentis could improve visual acuity, and maintain those vision improvements over the course of treatment when monthly therapy was administered. Ex. 2025; Ex. 2026. Given the historical challenges in effectively treating wAMD and the significant risk of permanent vision loss if treatment was delayed, the disclosure of these positive results swiftly impacted the community standard of care for wAMD.

66. In view of the results of the MARINA and ANCHOR trials, the PIER study sponsor recognized that a sham control arm was no longer acceptable and the study protocol was amended in February 2006 to allow control subjects to cross over to 0.5 mg ranibizumab for the remainder of the treatment period. Ex. 1026 at 2. In addition, in light of the highly disappointing first year results of the treatment arms, the PIER study organizers amended the treatment protocol in August of 2006 to allow all patients in the quarterly treatment arms to rollover and receive monthly injections of 0.5mg ranibizumab through the remainder of the study. Ex. 1026 at 2. In my experience as a clinical investigator, protocol amendments on this scale, in the middle of a study, are typically only implemented when there are serious safety

or efficacy concerns with drug or dosing regimen.

67. I note that in paragraph 111 of Dr. Wu's declaration, he suggests that fixed q4/q12 dosing of Lucentis (the Shams disclosure) was effective based on (1) the Lucentis 2006 label; and (2) the Regillo publication reporting first year results of the PIER Study. Ex. 1003, ¶ 111. I disagree with Dr. Wu's suggestion.

68. The Lucentis label was first approved by FDA for the treatment of wet AMD in 2006. The Dosage and Administration section of the label recommends monthly dosing of Lucentis: "LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month." Ex. 2028 at 2. Lucentis was not approved based on the Shams protocol or PIER data. Indeed, the Genentech Press Release that Dr. Wu cites in his declaration makes clear that "FDA approval of LUCENTIS is based on data from two large Phase III clinical trials (MARINA and ANCHOR)," which tested monthly injections of ranibizumab. Ex. 1006 at 2. The press release also notes: "In addition to data from the two pivotal studies, data from the Phase I/II FOCUS and Phase IIIb PIER studies were included in the FDA review." *Id.* The inclusion of PIER data in the Lucentis label does not suggest that q4/q12 Lucentis was an effective method of treating wet AMD. To the contrary, Lucentis' FDA-approved label reflects the concerns raised by both FDA and the study sponsor based on the results of the PIER trial. The label states "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 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. 2028 at 2. In addition, the clinical studies section of the Lucentis label (at §§ 14.1 and 14.2) shows the dramatic difference between the trial results in studies 1 and 2 (ANCHOR and MARINA), where patients gained visual acuity in the treatment arm during the study (see Figure 1) versus study 3 (PIER), where patients lost visual acuity in the treatment arm (see Figure 2). *Id.* at 7. An ordinarily skilled retinal specialist would not read the Lucentis label language as an FDA endorsement for fixed quarterly dosing of Lucentis. Rather, this language would be viewed as a warning to retina practitioners that this dosing regimen carriers a high risk for vision loss.

69. Dr. Wu selectively relies on a single sentence in the conclusion of the paper, that "Ranibizumab administered monthly for three months and then quarterly provided significant VA benefit to patients with AMD-related subfoveal CNV and was well tolerated." Ex. 1003 ¶ 111; Ex. 1026 at 1. But Dr. Wu's reliance on a single sentence in Regillo is misplaced. Regillo reports that both the treatment and control groups lost vision ("[t]he differences between the ranibizumab dose groups and the sham group in mean change in VA [visual acuity] from month three to month 12 were not statistically significant"). Ex. 1026 at 7. Regillo's comparison to sham

control ignores the fact that, by this point in time, losing less vision than sham control (no intervention), even if statistically significant, was not considered an effective treatment when MARINA and ANCHOR demonstrated average visual acuity gains with a monthly intravitreal dosing of ranibizumab. Genentech's amendment of the PIER study protocol to allow cross-over from sham, discussed above, reflects the community view that sham (or no intervention) was not an appropriate or ethical comparator by this point in time. Furthermore, Genentech's subsequent protocol amendment to allow all patients in the quarterly dosing arm to roll-over to monthly dosing of ranibizumab, as reported in the PIER Two Year Results, reflects the recognition that PIER quarterly dosing was ineffective as a method of treating an angiogenic eye disorder. Ex. 2016 at 2. Contrary to Dr. Wu's suggestion, an ordinarily skilled retinal specialist would not have understood that quarterly maintenance dosing of ranibizumab reported in Regillo to be an effective treatment regimen. Indeed, Regillo later concludes that "observations from the MARINA and ANCHOR trials suggest that the PIER regimen of dosing every three months after three monthly doses provides less benefit in VA on average than continued monthly dosing." Ex. 1026 at 9.

70. In light of Lucentis's FDA approval and the fact that retina practitioners could now maintain or even improve vision in their wAMD patients, fixed quarterly dosing that produced vision loss was not viewed as an acceptable or

effective treatment option. In my role as a key opinion leader, academic educator and expert clinician, I am very familiar with how retina specialists are trained and how they practice, particularly as it relates to intravitreal injections of VEGF inhibitors. I am not aware of any retinal specialists who have treated or presently treat their wAMD patients with fixed quarterly dosing of ranibizumab. In other words, I am not aware of any of my peers implementing the PIER regimen (Q4 followed by fixed Q12 dosing of ranibizumab) as a course of treatment for a patient with wet AMD.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe 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: April 14, 2021

Diana Do, MD

Diana V. Do, M.D.
Palo Alto, California

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner

Case PGR2021-00035
Patent 10,828,345

DECLARATION OF DAVID M. BROWN, M.D.

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I, Dr. David Brown, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. ("Regeneron") as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials I have reviewed in relation to the Petition for Post Grant review of U.S. Patent No. 10,828,345 (the "'345 patent") (Ex. 1001), in particular the state of the art as of the earliest filing date ("priority date") of the '345 patent and responses to the opinion and views of Petitioner's declarant, David Wu, M.D., Ph.D. I submit this declaration in support of Regeneron's Patent Owner Preliminary Response ("POPR").

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

II. QUALIFICATIONS AND EXPERIENCE

3. I am 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.

4. I graduated from Baylor College of Medicine with highest honors in 1988. I completed a medical/surgical internship at Baylor College of Medicine from 1989-1990. From 1990-1995, I completed ophthalmology and retina training at the University of Iowa where I was a Thomas Heed Fellow, 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.

5. 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,

6. 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" 2007-2021 and "Texas Super Docs" from 2009-2021. 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).

7. 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-VEGF agents for wet AMD ("wAMD"), retinal vein occlusion, and diabetic retinopathy.

8. I have served as a key investigator on the seminal Phase III clinical trials establishing the efficacy of anti-VEGF agents ranibizumab (Genentech's Lucentis) and aflibercept (Regeneron's Eylea) in wAMD, diabetic macular edema and diabetic retinopathy, and retinal vein occlusions. For example, I was a lead investigator on Genentech's Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) Study, the Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD (MARINA) Study, and Regeneron's VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW1) Study. 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. 2023.

III. SUMMARY OF OPINIONS

9. My opinions and views set forth in this declaration are based on my education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases, as well as the materials I reviewed in preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '345 patent at the time of its earliest priority application.

10. In forming my opinions, I have reviewed the following materials: (a) the Petition for Post Grant Review of the '345 patent, PGR2021-00035, including all cited exhibits, (b) all other documents and references herein, and (c) the Patent Owner's Preliminary Response to which my declaration relates.

11. For purposes of preparing this declaration in support of Patent Owner's Preliminary Response, I have been asked to apply Dr. Wu's definition of a person of ordinary skill in the art: a person with a medical doctorate, internship and residency in ophthalmology and either a 1-year medical retina fellowship or a 2-year vitreoretinal surgical fellowship. Ex. 1003 ¶ 82. Likewise, for purposes of preparing this declaration, I have been informed and understand that the earliest filing date of the '345 Patent is January 13, 2011, based on the filing of a Provisional Application on that date.

12. It is my opinion that by 2011, the person of ordinary skill in the art, would have understood that a fixed quarterly dosing regimen of ranibizumab, as disclosed in the Shams patent publication and corresponding PIER clinical trial, was a failure and not an effective method of treating an angiogenic eye disorder.

IV. STATE OF THE ART AS OF JANUARY 2011

A. Anti-VEGF Therapies for Angiogenic Eye Disorders

13. Angiogenic eye disorders, characterized by pathologic growth of abnormal blood vessels and vascular leakage from damaged blood vessels in the retina, present significant risks to patients' vision absent treatment. Angiogenic eye disorders, or neovascular eye diseases, include conditions such as iris neovascularization, retinal vein occlusion, diabetic retinopathy, diabetic macular edema, neovascular glaucoma, wAMD, and retinopathy of prematurity. Ex. 2004 at 23. A shared feature of angiogenic eye disorders is the presence of elevated ocular levels of VEGF, a molecule that plays a critical role in the pathology of angiogenesis and vascular permeability.

14. By January 2011, it was recognized by skilled retinal specialists, or the ordinarily skilled artisan, that treating patients with certain anti-VEGF agents, which reduce ocular VEGF levels, could reduce the incidence of pathologic angiogenesis and vascular permeability, and prevent loss of vision and even, in many cases, improve vision. Before the use of anti-VEGF agents, treatments for angiogenic eye

disorders included methods such as laser ablation and photodynamic therapy (PDT). These treatments generally did not improve vision in a clinically significant manner and often carried risks of further vision loss through, for example, scarring around the area of the choroidal neovascularization site targeted for treatment.

15. Of the angiogenic eye disorders, wAMD had a particularly poor prognosis, as vision loss in these patients could be sudden, severe, and irreversible. Laser and PDT treatments generally could only slow eventual vision loss. Unlike certain other angiogenic eye disorders such as diabetic macular edema and retinal vein occlusion, wAMD is less forgiving if patients wait too long to receive initial treatment or are not treated at sufficiently regular intervals. With wAMD, irreversible vision loss stems from a combination of retinal pigment epithelium ("RPE") rips, subretinal hemorrhages, and atrophy of the photoreceptors overlying the RPE, as well as fibrosis secondary to long-standing retinal and subretinal edema.

16. Early investigation of anti-VEGF agents to treat wAMD included the use of pegaptanib (Macugen) and investigation of the use of off-label injections of Genentech's VEGF antibody drug bevacizumab (Avastin). The major clinical experimentation that established for the retinal community the efficacy of anti-VEGF therapy, however, came with Genentech's drug, ranibizumab (Lucentis), a VEGF antibody fragment designed to be injected intravitreally into the patient's eye at regular intervals.

17. In 2003, Genentech began two large-scale, randomized Phase III clinical trials to test monthly ranibizumab injections in patients with wAMD — MARINA and ANCHOR. I served as a principal investigator for both of these studies and was the first author on the NEJM primary manuscript for ANCHOR, (Brown DM, et al., *Ranibizumab versus verteporfin for neovascular age-related macular degeneration*. N Engl J Med. 2006 Oct 5;355(14):1432-44) (Ex. 2026) and second author on the NEJM primary manuscript for MARINA (Rosenfeld PJ, Brown DM, et al., *Ranibizumab for neovascular age-related macular degeneration*. N Engl J Med. 2006 Oct 5;355(14):1419-31) (Ex. 2025).

18. The MARINA trial ran from March of 2003 to December 2005 and enrolled 716 patients with wAMD with either minimally classic or occult choroidal neovascularization. Ex. 2025 at 1. Patients were randomly assigned to received 24 monthly intravitreal injections of Lucentis (either 0.3 mg or 0.5 mg) or sham injections. *Id.* The primary endpoint of the study was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

19. One year results of the MARINA trial were presented by Genentech in July of 2005. Ex. 2031. The results showed that nearly ninety-five percent of patients treated with Lucentis maintained or improved vision at 12 months. *Id.* The two-year results of the MARINA trial were then published in the New England Journal of Medicine on October 5, 2006. Ex. 2025 at 1. The mean improvements

in vision demonstrated in the first 12 months of the study were sustained through the second years of study. *Id.* Mean increases in visual acuity were +6.5 letters in the 0.3 mg group and +7.2 letters in the 0.5 mg groups, compared with a decrease of -10.3 letters in the sham-injection group. *Id.* Impressively, visual acuity improved by 15 or more letters in 24.8% of the 0.3 mg group and 33.8% of the 0.5 mg group. *Id.*

20. 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, 2 months before the end of the patient's final study visit at 24 months, that all patients 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 the hope for sustained improvements in visual acuity.

21. The MARINA results were supplemented by the outcomes from the ANCHOR trial. The ANCHOR trial ran from May of 2003 to September of 2006 and enrolled 423 patients with predominantly classic choroidal neovascularization in wAMD. Ex. 2026 at 1. Patients 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 primary endpoint of the study was also the proportion of patients losing fewer than 15 letters

from baseline visual acuity at 12 months. *Id.*

22. One year results of the ANCHOR trial were presented by Genentech in November of 2005. Ex. 2031. Preliminary one-year data showed that approximately 94 percent of patients treated with 0.3 mg of Lucentis and 96 percent of those treated with 0.5 mg of Lucentis maintained or improved vision compared to approximately 64 percent of those treated with PDT alone. *Id.* The one-year results were published in the New England Journal of Medicine on October 5, 2006, a paper on which I served as the first author. Ex. 2026 at 1. The two-year results of ANCHOR were then published in January 2009 in Ophthalmology. Ex. 2027 at 1. In the ANCHOR study, 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. 2027 at 1. Impressively, visual acuity improved by 15 or more letters in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group. *Id.*

23. 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. 2027 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 ranibizumab treatment arms resulted in a protocol amendment that allowed patients in the PDT-alone arm of the study to cross over to ranibizumab injections during the latter part of the study. *Id.* at 4.

24. Based on this data from MARINA and ANCHOR, Lucentis received FDA approval for the treatment of wAMD in June 2006. Ex. 1006 at 2. By this point in time, it was well established in the retinal community that standard of care had moved beyond observation and monitoring for wAMD (which was utilized as a sham control) to continuous intravitreal injections of ranibizumab (or off-label Avastin), which were effective methods for improving patients' vision compared to baseline, and often maintained those gains over the course of treatment.

B. Extended Dosing Goals

25. While MARINA and ANCHOR demonstrated powerful breakthroughs in the treatment of wAMD, a persistent goal of the retinal community was to find an effective treatment regimen that required less than monthly visits to an ophthalmologist to treat and/or monitor the progression of wAMD. Intravitreal injections, while generally safe, present the risk of rare but serious adverse events such as endophthalmitis, severe intraocular inflammation, and retinal detachment. Further, monthly visits for injections are costly and burdensome to patients. Even simple monthly monitoring, while reducing risk from IVT injections themselves, is

burdensome, as patients with wAMD are typically elderly and in-person visits present a challenge for the patient and their caretakers.

26. By 2011, the field continued to investigate extended dosing regimens to treat angiogenic eye disorders. As Jeffrey Heier, M.D., a colleague and co-investigator in the Regeneron Phase III wAMD trials noted: "Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits." Ex. 2021 at 9. Despite these efforts, before 2011, studies showed "fixed quarterly or 'as needed' (*pro re nata* [PRN]) dosing regimens, without requiring monthly monitoring visits, were not effective at maintaining vision." *Id.* at 1.

27. One such study was Genentech's PIER study. The PIER Study 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. 1026. at 2. I participated as a clinical investigator and was part of the PIER Study Group, and was 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 ranibizumab over an extended treatment period was not an effective method of treatment.

28. It was not until the clinical trial results from VIEW I and VIEW II, Regeneron's Phase III trials of aflibercept in wAMD, were released that an anti-VEGF inhibitor demonstrated the ability to provide a safe and highly effective treatment for wAMD on an extended fixed dosing regimen. The VIEW trials compared intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, 2 mg every 2 months after 3 initial monthly doses, and ranibizumab 0.5 mg monthly. Ex. 2021 at 1. The primary endpoint of the VIEW trials was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters). *Id.* The one-year results from the VIEW trials demonstrated that intravitreal aflibercept dosed either monthly or every two months after the three initial loading doses produced similar efficacy outcomes on average to monthly ranibizumab. *Id.* This finding of the VIEW trials was viewed with excitement across the retina community. As Heier 2012 noted: "[T]he finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians." *Id.* at 10.

V. SHAMS DISCLOSED AN UNSUCCESSFUL 12-WEEK DOSING REGIMEN

29. I have reviewed Shams' disclosure (Ex. 1004) and recognize that the Trial Design (Figure 1) and Treatment Schema (Figure 2) set forth in Shams, as well

as its description of a dosing regimen in Example 1, all correspond to Genentech's PIER Study, a clinical trial of ranibizumab (Lucentis®). *Compare* Ex. 1004, Figure 2, *with* Ex. 1026 at 2.

30. Figure 2 of Shams illustrates the administration of the "first individual doses" at months 0, 1, and 2, followed by the "secondary doses" at months 5, 8, 11, and continuing every 3 months through 24 months. Ex. 1004, Figure 2. This corresponds precisely to the study arm in PIER: "The ranibizumab groups received their assigned dose by intravitreal injection every month for three doses (day zero, months one and two), followed by doses every three months (months five, eight, 11, 14, 17, 20, and 23)." Ex. 1026 at 2.

31. 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-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. 1026 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. Ex. 1026 at 7 (Figure 2).

32. 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. 1026 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. 2018 at 4.

33. 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.*, the assessment time point for the primary analysis). Ex. 2016 at 2. As explained *supra*, the 12-month data from MARINA and ANCHOR had established to the retinal community that it would be in the best interest of the sham groups of patients to be treated with ranibizumab, rather than be put further at risk for severe, irreversible vision loss under an observation-only scheme.

34. The second protocol amendment was the direct result of the review of

the 12-month PIER data. 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. 2016 at 2. The second year of the PIER study was functionally designed to be confirmatory of fixed quarterly dosing's efficacy, and given the 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.

35. The year-two results from PIER confirmed the lack of efficacy of the dosing regimen. The 0.3 mg ranibizumab group saw a mean loss 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. 2016 at 2. 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 and prevent blindness.

36. 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. 2020 at 3, 7. Macular hemorrhages are a hallmark of 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 poor visual prognosis in a majority of cases." *Id.* at 1. It was a serious concern, therefore, that quarterly dosing did not even 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.

37. 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. 2017 at 1; *id.* at 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. 2018 at 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. Reducing the frequency of injections should, therefore, be done with caution."); Ex. 2015 ("The PIER data have led Genentech to recommend that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing.")

38. 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. 1006 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 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. 2028.

39. In my opinion, FDA's review and consideration of the PIER results, and this language in the label, would not suggest to the person of ordinary skill that quarterly maintenance dosing was an effective or acceptable option for a treatment regimen for a patient with an angiogenic eye disorder, such as wAMD.

40. I disagree with Dr. Wu's suggestion in paragraph 111 that this language in the FDA label would indicate that the Shams/PIER regimen would have been a longer than monthly dosing regimen utilized by those in the art. Ex. 1003, ¶ 111.

Indeed, Dr. Wu does not address the label's explicit note that this is a "less effective" regimen than fixed monthly, and that it "will lead" to a "loss of visual acuity benefit." Ex. 2028 at 2. Rather, it is my understanding that FDA would present a comprehensive look at the clinical data it is presented with when issuing approval guidelines, and indeed the clinical studies section of the Lucentis label (at §§ 14.1 and 14.2) plainly shows the drastic disparity between the study results from ANCHOR and MARINA and those of PIER. *Id.* at 7. Figure 1 shows that Lucentis 0.5 mg arm in Study 1 (MARINA) had mean changes in visual acuity of +6.6 letters at 24 months, and Lucentis 0.5 mg arm in Study 2 (ANCHOR) had +11.3 letters mean changes at 24 months, while Figure 2 shows Lucentis 0.5 mg arm in Study 3 (PIER) had a mean change of -0.2 letters at 12 months. *Id.* at 7. The import of these Figures would be clear to retina practitioners: the fixed quarterly dosing regimen of PIER carriers a high risk for permanent vision loss.

41. I also disagree with Dr. Wu's suggestion in paragraph 63 that the EXCITE study "was consistent with the findings in PIER in that both monthly and quarterly dosing of ranibizumab was able to improve vision of wet AMD patients." Ex. 1003 ¶ 63. As an initial matter, it is incorrect to suggest that the PIER study found quarterly dosing to "improve vision of wet AMD patients." A finding of superiority to sham is not equated with improved vision; in the context of the PIER Study, it simply meant that patients in the ranibizumab treatment arms lost less

vision at the 12 and 24 month endpoints as compared to baseline vision than sham. True vision improvement for wAMD patients occurred in ANCHOR and MARINA, where there were significant visual acuity gains compared to baseline at 12 and 24 months.

42. Further, Dr. Wu fails to address the fact that the objective of the EXCITE study, conducted from December 2005 to January 2008, was to demonstrate the "noninferiority of a quarterly treatment regimen to a monthly regimen of ranibizumab in patients" with subfoveal CNV secondary to wAMD; and that "noninferiority of a quarterly regimen was not achieved with reference to 5.0 letters." Ex. 1027 at 1. In other words, this study was a failure by its own terms. Like PIER, the treatment arms of EXCITE were administered as three monthly loading doses prior to fixed quarterly doses of ranibizumab, and also like PIER, EXCITE demonstrated losses of initial visual acuity gains after patients moved to quarterly injections. *Id.* at 5. The study group concluded: "The direct comparative analysis between monthly and quarterly treatment regimens of the EXCITE study is consistent with the clinical guidance on ranibizumab treatment, which recommends rigorous monthly monitoring with timely retreatment of patients with recurrent disease activity to achieve the best treatment outcomes for patients." *Id.* at. 8.

43. In my role as a key opinion leader in the treatments for angiogenic eye disorders, as well as an active clinician and clinical instructor, I am very familiar

with the standards for how retina specialists are trained, best clinical practices, and how in fact retina doctors treat patients. As of 2011, following the disclosure of the PIER results and the post hoc analyses presented in peer reviewed publications, due to the dismal one-year visual acuity results and the unacceptable risks of permanent vision loss, retinal specialists would not have implemented the PIER dosing regimen (Q4 followed by fixed Q12 dosing of ranibizumab) as a course of treatment for a patient with an angiogenic eye disorder. After the results of PIER were presented and published, I am not aware of any retina specialist who recommends or has treated patients on a fixed q4/q12 quarterly dosing regimen of ranibizumab, and I believe from a medical malpractice standpoint, that such treatment would be inconsistent with the community standard of care.

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

Dated: Apr 14, 2021

David M. Brown, M.D.

Austin, Texas

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VEGF-TRAP$_{R1R2}$ Suppresses Choroidal Neovascularization and VEGF-Induced Breakdown of the Blood–Retinal Barrier

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Vascular endothelial growth factor (VEGF) plays a central role in the development of retinal neovascularization and diabetic macular edema. There is also evidence suggesting that VEGF is an important stimulator for choroidal neovascularization. In this study, we investigated the effect of a specific inhibitor of VEGF, VEGF-TRAP$_{R1R2}$, in models for these disease processes. VEGF-TRAP$_{R1R2}$ is a fusion protein, which combines ligand binding elements taken from the extracellular domains of VEGF receptors 1 and 2 fused to the Fc portion of IgG1. Subcutaneous injections or a single intravitreous injection of VEGF-TRAP$_{R1R2}$ strongly suppressed choroidal neovascularization in mice with laser-induced rupture of Bruch's membrane. Subcutaneous injection of VEGF-TRAP$_{R1R2}$ also significantly inhibited subretinal neovascularization in transgenic mice that express VEGF in photoreceptors. In two models of VEGF-induced breakdown of the blood–retinal barrier (BRB), one in which recombinant VEGF is injected into the vitreous cavity and one in which VEGF expression is induced in the retina in transgenic mice, VEGF-TRAP$_{R1R2}$ significantly reduced breakdown of the BRB. These data confirm that VEGF is a critical stimulus for the development of choroidal neovascularization and indicate that VEGF-TRAP$_{R1R2}$ may provide a new agent for consideration for treatment of patients with choroidal neovascularization and diabetic macular edema. J. Cell. Physiol. 195: 241–248, 2003. © 2003 Wiley-Liss, Inc.

Ocular neovascularization, consisting of retinal and choroidal neovascularization, is an enormous public health problem. Retinal neovascularization occurs in ischemic retinopathies, the most prevalent of which is diabetic retinopathy, the most common cause of severe vision loss in young people in developed countries (Klein et al., 1984). Choroidal neovascularization complicates several diseases in which there are abnormalities of the Bruch's membrane/retinal pigmented epithelial (RPE) cell complex, such as age-related macular degeneration (AMD), the most common cause of severe vision loss in the elderly (The Macular Photocoagulation Study Group, 1991). While retinal and choroidal neovascularization are responsible for the vast majority of severe vision loss in Americans, diabetic macular edema is the major cause of moderate vision loss (Klein et al., 1984).

Multiple stimulatory factors may contribute to the development of retinal neovascularization, but vascular endothelial growth factor (VEGF) plays a critical role. Signaling through VEGF receptors is both necessary and sufficient for development of retinal neovascularization (Okamoto et al., 1997; Seo et al., 1999; Ozaki et al., 2000). VEGF also causes breakdown of the blood–retinal barrier (BRB) (Ozaki et al., 1997), and has been implicated in the early breakdown of the BRB that occurs in diabetes (Qaum et al., 2001). In addition, VEGF is also an important stimulus for choroidal neovascularization (Kwak et al., 2000). Therefore, antagonizing VEGF is a potentially useful strategy for several ocular diseases.

Many approaches for antagonizing VEGF are being considered. One strategy is to inject relatively large inhibitors, such as aptamers or FAb fragments of anti-VEGF antibodies directly into the eye. Phase I clinical

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trials testing the safety and tolerability of this approach have been completed and phase II and III trials are planned or in progress. Preliminary reports suggest that inflammation may occur following intraocular injection of antibodies or aptamers, but this has not been a severe enough problem to discontinue evaluation of these approaches (Guyer et al., 2001; Schwartz et al., 2001). This approach has some concerns, because repeated intraocular injections carry risks of retinal detachment and endophthalmitis, and may not be feasible depending upon the frequency of injections required. Another strategy is to avoid repeated intraocular injections by systemic administration of small molecule VEGF antagonists (Seo et al., 1999; Kwak et al., 2000; Ozaki et al., 2000). There is a theoretical concern that some beneficial types of angiogenesis, such as collateral formation in ischemic myocardium, may be inhibited. But there are no data to support this concern and it is equally plausible that systemic inhibition of VEGF could have many additional benefits, since angiogenesis has been implicated in tumor growth, atherosclerosis, and arthritis (for review, see Folkman, 1995). Oral administration of VEGF receptor kinase inhibitors results in dramatic suppression of retinal and choroidal neovascularization and is a very promising approach (Seo et al., 1999; Kwak et al., 2000; Ozaki et al., 2000). These agents are selective, but not specific VEGF antagonists, because it is difficult to inhibit VEGF receptor kinases without inhibiting homologous kinases such as platelet-derived growth factor (PDGF) receptor kinase and c-kit, the receptor for stem cell factor (Fabbro et al., 1999; Bold et al., 2000; Drevs et al., 2000; Wood et al., 2000). The effects of these additional activities are unknown and while they are being investigated, it is prudent to consider and test more selective VEGF inhibitors.

Soluble VEGF receptors provide a very specific way to antagonize VEGF, and several studies have demonstrated that the extracellular domain of VEGF receptor 1 (VEGF-R1) has antiangiogenic activity (Goldman et al., 1998; Kong et al., 1998; Honda et al., 2000; Shiose et al., 2000; Takayama et al., 2000; Lai et al., 2001; Mahasreshti et al., 2001; Bainbridge et al., 2002; Lai et al., 2002). A disadvantage of soluble VEGF-R1 is that it is cleared fairly rapidly. Pharmacokinetic properties can be improved by linking the ligand binding domains of VEGF receptors to the Fc portion of IgG, which slows clearance by conferring the long circulating half-life of an antibody to the chimeric molecule. A potential trade off is that the relatively large size of such constructs could limit tissue penetration from the systemic circulation, which is a particularly important consideration for treatment of ocular diseases. In this study, we have evaluated both local and systemic administration of a novel chimeric molecule, VEGF-$TRAP_{R1R2}$, which comprises portions of the extracellular domain of VEGFR-1 (flt-1) and VEGFR-2 (KDR), in models of ocular neovascularization and breakdown of the BRB.

MATERIALS AND METHODS

VEGF-$TRAP_{R1R2}$

VEGF-$TRAP_{R1R2}$ (Regeneron Pharmaceuticals, Tarrytown, NY) is a recombinant fusion protein that contains Ig domain 2 of VEGF-R1 and Ig domain 3 of VEGF-R2 fused to the Fc portion of human IgG1 (Wulff et al., 2002). VEGF-$TRAP_{R1R2}$ binds VEGF with high affinity (kD $\approx$ 1 pM) and subcutaneous injection of 25 mg/kg of VEGF-$TRAP_{R1R2}$ has been shown to effectively neutralize VEGF in mice with VEGF-secreting tumors (Wong et al., 2001). Recombinant human Fc was used as a control protein.

Treatment of mice with laser-induced choroidal neovascularization

Choroidal neovascularization was generated by modification of a previously described technique (Tobe et al., 1998b). Briefly, 4–5-week-old female C57BL/6J mice were anesthetized with ketamine hydrochloride (100 mg/kg body weight) and the pupils were dilated with 1% tropicamide. Three burns of 532 nm diode laser photocoagulation (75 μm spot size, 0.1 sec duration, 120 mW) were delivered to each retina using the slit lamp delivery system of an OcuLight GL Photocoagulator (Iridex, Mountain View, CA) and a hand held cover slide as a contact lens. Burns were performed in the 9, 12, and 3 o'clock positions of the posterior pole of the retina. Production of a bubble at the time of laser, which indicates rupture of Bruch's membrane, is an important factor in obtaining CNV (Tobe et al., 1998b), so only burns in which a bubble was produced were included in the study. Mice were treated with subcutaneous injections of 25 mg/kg of VEGF-$TRAP_{R1R2}$ or Fc fragment 1 day prior to laser and on days 2, 5, 8, and 11 after laser. At 14 days after laser, the mice were euthanized, serum was collected and stored, and eyes were rapidly dissected for choroidal flat mounts or frozen in optimum cutting temperature embedding compound (OCT; Miles Diagnostics, Elkhart, IN).

Some mice were given intraocular injection of 4.92 μg of VEGF-$TRAP_{R1R2}$ in one eye and 4.92 μg Fc fragment in the other eye. Two weeks later, mice were perfused with fluorescein-labeled dextran and choroidal neovascularization was measured.

Quantitative analysis of the amount of choroidal neovascularization

The sizes of CNV lesions were measured in choroidal flat mounts (Edelman and Castro, 2000) by an investigator masked with respect to treatment group. Mice used for the flat mount technique were anesthetized and perfused with 1 ml of phosphate-buffered saline containing 50 mg/ml of fluorescein-labeled dextran (2×10^6 average mw, Sigma, St. Louis, MO) as previously described (Tobe et al., 1998a). The eyes were removed and fixed for 1 h in 10% phosphate-buffered formalin. The cornea and lens were removed and the entire retina was carefully dissected from the eyecup. Radial cuts (4–7, average 5) were made from the edge to the equator and the eyecup was flat mounted in Aquamount with the sclera facing down. Flat mounts were examined by fluorescence microscopy on an Axioskop microscope (Zeiss, Thornwood, NY) and images were digitized using a 3 color CCD video camera (IK-TU40A, Toshiba, Tokyo, Japan) and a frame grabber. Image-Pro Plus software (Media Cybernetics, Silver Spring, MD) was used to measure the total area of choroidal neovascularization associated with each burn with the operator masked with respect to treatment group. Statistical comparisons were made between the size of lesions in mice

treated with VEGF-TRAP$_{R1R2}$ versus those in mice treated with Fc fragment by two-tailed *t*-test. In addition, the average size of choroidal neovascularization in each mouse was calculated and plotted against the serum level of VEGF-TRAP$_{R1R2}$ obtained by ELISA.

In some mice, the eyes were rapidly removed and frozen in optimum cutting temperature embedding compound (OCT; Miles Diagnostics). Ten μm frozen sections were cut through entire lesions and the sections were histochemically stained with biotinylated *Griffonia simplicifolia* lectin B4 (GSA, Vector Laboratories, Burlingame, CA), which selectively binds to vascular cells. Slides were incubated in methanol/H_2O_2 for 10 min at 4°C, washed with 0.05 M Tris-buffered saline, pH 7.6 (TBS), and incubated for 30 min in 10% normal porcine serum. Slides were incubated 2 h at room temperature with biotinylated GSA and after rinsing with 0.05 M TBS, they were incubated with avidin coupled to peroxidase (Vector Laboratories) for 45 min at room temperature. The slides were developed with Histo-Mark Red (Kirkegaard and Perry, Cabin John, MD) to give a red reaction product and counter stained with Contrast Blue (Kirkegaard and Perry).

Transgenic mice with increased expression of VEGF in photoreceptors

Transgenic mice with VEGF driven by the rhodopsin promoter develop subretinal neovascularization due to expression of VEGF in photoreceptors beginning at about P7 (Okamoto et al., 1997). Hemizygous transgene-positive mice were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment at P7, P10, P13, P16, and P19. At P21, the mice were sacrificed and the amount of subretinal neovascularization was quantified as previously described (Tobe et al., 1998a). Briefly, mice were anesthetized and perfused with 1 ml of phosphate-buffered saline containing 50 mg/ml of fluorescein-labeled dextran (2×10^6 average mw, Sigma). The eyes were removed and fixed for 1 h in 10% phosphate-buffered formalin. The cornea and lens were removed and the entire retina was carefully dissected from the eyecup, radially cut from the edge of the retina to the equator in all 4 quadrants, and flat-mounted in Aquamount with photoreceptors facing upward. The retinas were examined by fluorescence microscopy at 200x magnification, which provides a narrow depth of field so that when focusing on neovascularization on the outer surface of the retina, the remainder of the retinal vessels are out-of-focus allowing easy delineation of the neovascularization. The outer edge of the retina, which corresponds to the subretinal space in vivo, is easily identified and therefore there is standardization of focal plane from slide to slide. Images were digitized using a 3 CCD color video camera and a frame grabber. Using Image-Pro Plus software, an investigator masked with respect to treatment group delineated each of the lesions and calculated the total area of neovascularization per retina as previously described (Tobe et al., 1998a).

VEGF-induced breakdown of the BRB

Adult C57BL/6 mice were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc and on the following day VEGF-induced breakdown of the BRB was quantified as previously reported (Derevjanik et al., 2002). Mice were anesthetized with 25 mg/kg of ketamine and 4 mg/kg of xylazine, pupils were dilated with 1% tropicamide. Intraocular injections were performed with a Harvard pump microinjection apparatus and pulled glass micropipets (Mori et al., 2001). Each micropipet was calibrated to deliver 1 μl of fluid upon depression of a foot switch. Under a dissecting microscope, the sharpened tip of a micropipet was passed through the sclera just behind the limbus into the vitreous cavity, and the foot switch was depressed injecting 1 μl of 10^{-6} M human vascular endothelial growth factor (VEGF; R&D Systems, Minneapolis, MN). Six hours later, retinal vascular permeability was measured using [^{3}H]mannitol as a tracer.

Double transgenic rho/rtTA-TRE/VEGF mice with doxycycline-inducible expression of VEGF in photoreceptors (Ohno-Matsui et al., 2002) were also used. Double transgenics were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment of IgG and on the following day they were started on 2 mg/ml of doxycycline in their drinking water. The next day they were given a second subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and after two days, retinal vascular permeability was measured.

Measurement of BRB breakdown using [^{3}H]mannitol as tracer

Six hours after intraocular injection of VEGF in wild type mice or 2 days after rho/rtTA-TRE/VEGF were started on doxycycline, mice were given an intraperitoneal injection of 1 μCi/gram body weight of [^{3}H]mannitol (New England Nuclear, Boston, MA). After 1 h, mice were sacrificed and eyes were removed. The cornea and lens were removed and the entire retina was carefully dissected from the eyecup and placed within pre-weighed scintillation vials. The thoracic cavity was opened and the left superior lobe of the lung was removed and placed in another pre-weighed scintillation vial. All liquid was removed from the vials and remaining droplets were allowed to evaporate over 20 min. The vials were weighed and the tissue weights were recorded. One ml of NCSII solubilizing solution (Amersham, Chicago, IL) was added to each vial and the vials were incubated overnight in a 50°C water bath. The solubilized tissue was brought to room temperature and decolorized with 20% benzoyl peroxide in toluene in a 50°C water bath. The vials were brought to room temperature and 5 ml of Cytoscint ES (ICN, Aurora, OH) and 30 μl of glacial acetic acid were added. The vials were stored for several hours in darkness at 4°C to eliminate chemoluminescence. Radioactivity was counted with a Wallac 1409 Liquid Scintillation Counter (Gaithersburg, MD).

RESULTS

Subcutaneous injection of VEGF-TRAP$_{R1R2}$ inhibits choroidal neovascularization

Bruch's membrane was ruptured at 3 locations in each eye by laser photocoagulation in C57BL/6 mice. One day prior to laser and on days 2, 5, 8, and 11 after laser, mice received subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment. Retinal whole mounts from fluorescein dextran-perfused mice treated with VEGF-

$TRAP_{R1R2}$ (Fig. 1A,B) had areas of neovascularization that were much smaller than those seen in mice treated with Fc fragment (Fig. 1C,D). Sections through Bruch's membrane rupture sites in other mice treated with VEGF-$TRAP_{R1R2}$ showed complete or near-complete inhibition of choroidal neovascularization (Fig. 1E,F). Mice treated with Fc fragment (Fig. 1G,H) had choroidal neovascularization similar to that seen in mice treated with vehicle in several other studies (Seo et al., 1999; Kwak et al., 2000). Measurement of the area of choroidal neovascularization by image analysis confirmed that there was significantly less neovascularization in eyes treated with VEGF-$TRAP_{R1R2}$ compared to those treated with Fc fragment (Fig. 1I). The level of VEGF-$TRAP_{R1R2}$ was measured in plasma obtained from each of the mice at the time of sacrifice. Each of the mice that had been injected with Fc fragment had no detectable VEGF-$TRAP_{R1R2}$ in its plasma, while mice that had been injected with VEGF-$TRAP_{R1R2}$ had plasma levels ranging from 57 to 205 μg/ml. All of the plasma levels of VEGF-$TRAP_{R1R2}$ between 57 and 205 μg/ml were associated with strong inhibition of choroidal neovascularization (Fig. 1J).

Immediately after laser, some mice were given intraocular injection of VEGF-$TRAP_{R1R2}$ or Fc fragment of IgG. Two weeks later, mice were perfused with fluorescein-labeled dextran and choroidal neovascularization was measured. Mice that received intraocular

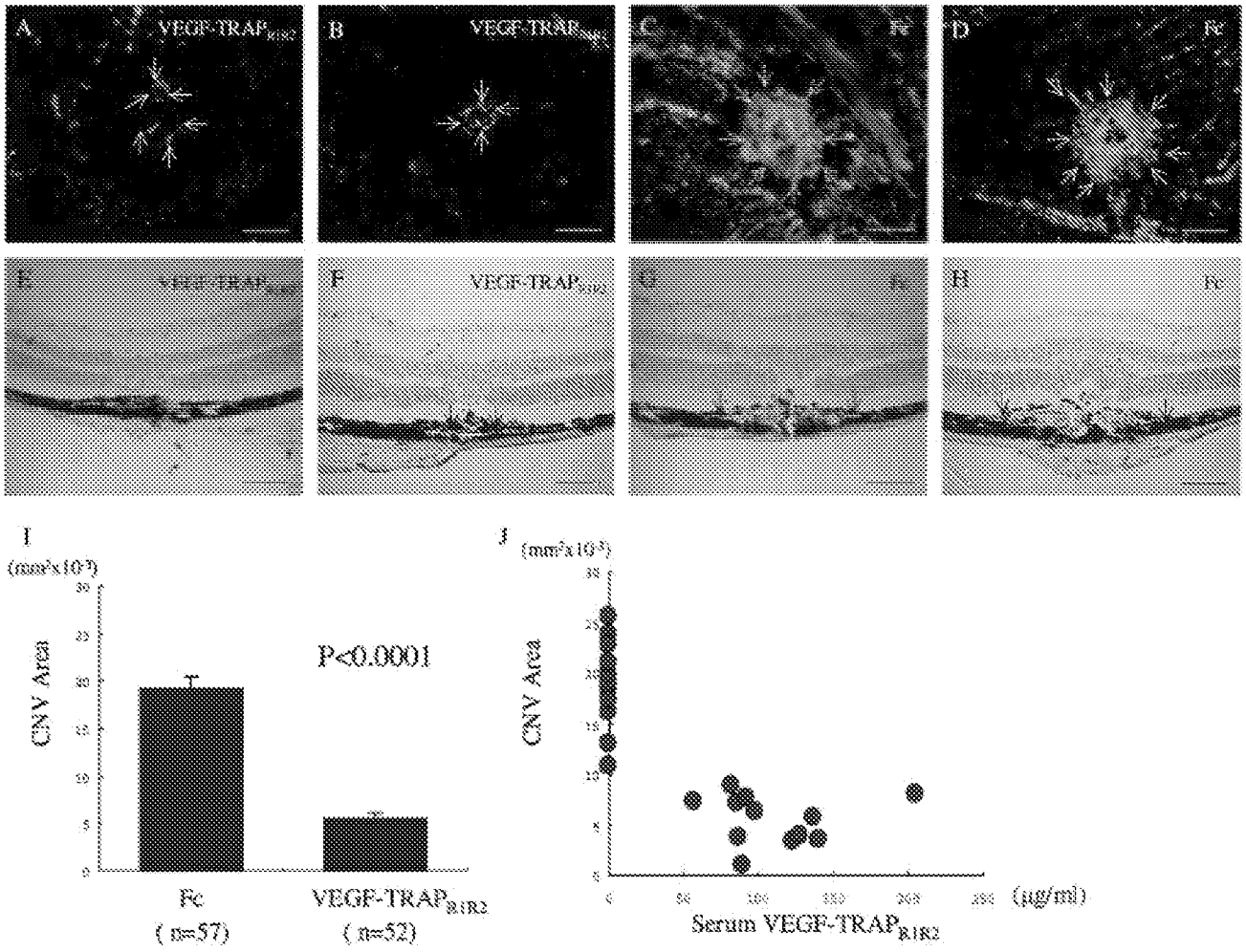

Fig. 1. Subcutaneous VEGF-$TRAP_{R1R2}$ suppresses choroidal neovascularization at sites of rupture of Bruch's membrane. Adult C57BL/6 mice were had rupture of Bruch's membrane by laser photocoagulation in 3 locations in each eye. Prior to laser and on days 2, 5, 8, and 11 after laser, mice received subcutaneous injection of 25 mg/kg of VEGF-$TRAP_{R1R2}$ or Fc fragment of IgG. Parts **A** and **B** show small areas of neovascularization (surrounded by arrows) in retinal whole mounts from two fluorescein dextran-perfused mice treated with VEGF-$TRAP_{R1R2}$. *Griffonia simplicifolia* (GSA) lectin-stained sections in two other mice treated with VEGF-$TRAP_{R1R2}$ show minimal choroidal neovascularization (**E**- none visible and **F**- between arrows). Parts **C** and **D** show large areas of neovascularization (surrounded by arrows) in choroidal flat mounts from two Fc fragment-treated mice and GSA-stained sections from two other mice treated with Fc fragment show prominent areas of neovascularization (**G** and **H**, between arrows). Measurement by image analysis of the area of neovascularization on choroidal flat mounts (**I**) showed an average area that was significantly smaller ($P < 0.0001$ by Student's two-tailed t-test) in VEGF-$TRAP_{R1R2}$-treated mice (20 eyes, 52 rupture sites) compared to Fc-treated mice (20 eyes, 57 rupture sites). Plasma levels of VEGF at the time of sacrifice determined by ELISA plotted against the average area of choroidal neovascularization per mouse showed marked suppression of neovascularization at all plasma levels between 50 and 200 μg/ml (**J**). Bar = 100 μm.

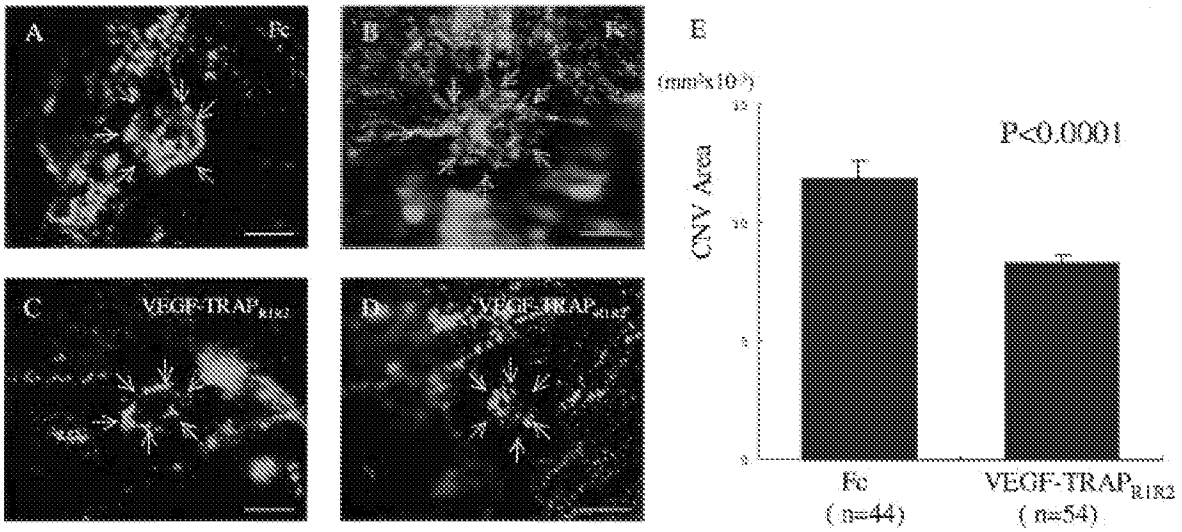

Fig. 2. A single intravitreous injection of VEGF-TRAP$_{R1R2}$ suppresses choroidal neovascularization at Bruch's membrane rupture sites. Immediately after laser, C57BL/6 mice were given intraocular injection of 4.92 μg of VEGF-TRAP$_{R1R2}$ in one eye and 4.92 μg of Fc fragment in the other eye. Two weeks later, mice were perfused with fluorescein-labeled dextran and choroidal neovascularization was measured. **A** and **B**: Large areas of neovascularization (surrounded by arrows) are seen in flat mounts from two separate mice treated with intravitreous injection of Fc fragment. **C** and **D**: Small areas of neovascularization (surrounded by arrows) are seen in two separate mice given a single intravitreous injection of VEGF-TRAP$_{R1R2}$. **E**: The area of choroidal neovascularization measured by image analysis was significantly less ($P < 0.0001$; Student's two-tailed t-test) in VEGF-TRAP$_{R1R2}$-treated eyes (19 eyes, 54 rupture sites) compared to Fc-treated eyes (19 eyes, 44 rupture sites). Bar = 100 μm

injection of Fc fragment had larger areas of choroidal neovascularization (Fig. 2A,B) than those seen in mice that received a single intraocular injection of VEGF-TRAP$_{R1R2}$ (Fig. 2C,D). There was a statistically significant reduction in the mean area of neovascularization in VEGF-TRAP$_{R1R2}$-injected eyes compared to Fc fragment-injected eyes (Fig. 2E).

VEGF-TRAP$_{R1R2}$ inhibits subretinal neovascularization in Rho/VEGF transgenic mice

Rho/VEGF transgenic mice express VEGF in photoreceptors starting about postnatal day (P) 7 resulting in extensive subretinal neovascularization by P21

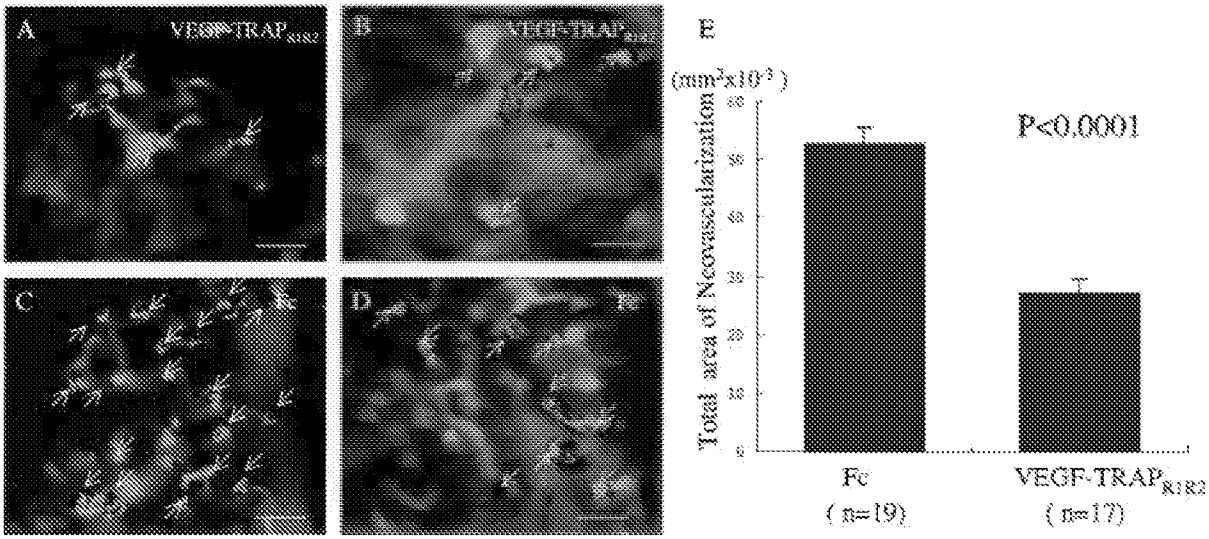

Fig. 3. Subcutaneous VEGF-TRAP$_{R1R2}$ inhibits subretinal neovascularization in rho/VEGF transgenic mice. Rho/VEGF transgenic mice begin to express VEGF in photoreceptors about postnatal day (P) 7. At P7, mice were divided into two groups and treated with 25 mg/kg of VEGF-TRAP$_{R1R2}$ (9 mice, 17 eyes) or Fc fragment (10 mice, 19 eyes) on P7, P10, P13, P16, and P19, and on P21, the mice were anesthetized and perfused with fluorescein-labeled dextran. Retinal whole mounts from mice treated with VEGF-TRAP$_{R1R2}$ showed few areas of neovascularization (**A** and **B**, arrows), while there were numerous clumps of new vessels in the subretinal space of mice that had been treated with Fc fragment (**C** and **D**, arrows). Measurement of the total area of neovascularization per retina by image analysis showed significantly less neovascularization in VEGF-TRAP$_{R1R2}$-treated mice, compared to those treated with Fc fragment (**E**). Bar = 100 μm.

(Okamoto et al., 1997; Tobe et al., 1998a). Rho/VEGF mice received subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment of IgG on P7, P10, P13, P16, and P19, and on P21, they were perfused with fluorescein-labeled dextran. Mice treated with VEGF-TRAP$_{R1R2}$ had very few clumps of neovascularization (Fig. 3A,B, arrows), while there were numerous clumps of new vessels in the subretinal space of mice that had been treated with Fc fragment of IgG (Fig. 3C,D, arrows). Image analysis showed that mice treated with VEGF-TRAP$_{R1R2}$ had an average area of neovascularization per retina that was significantly smaller total area than mice treated with Fc fragment (Fig. 3E).

VEGF-TRAP$_{R1R2}$ inhibits VEGF-induced breakdown of the BRB

Adult C57BL/6 mice were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and on the following day received an intravitreous injection of 1 μg of 10^{-6} M VEGF. Six hours later, retinal vascular permeability was measured using [^{3}H]mannitol as a tracer. Mice treated with VEGF-TRAP$_{R1R2}$ had a significantly smaller retina to lung leakage ratio than mice treated with Fc fragment of IgG indicating less breakdown of the BRB (Fig. 4A).

We have previously produced and characterized double transgenic mice with doxycycline-inducible expression of VEGF in the retina (Ohno-Matsui et al., 2002). Double transgenics were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and on the following day they were started on 2 mg/ml of doxycycline in their drinking water. Two days later, they were given a second subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and then the next day retinal vascular permeability was measured with [^{3}H]mannitol. Double transgenic mice treated with VEGF-TRAP$_{R1R2}$ had a significant reduction in the retina to lung leakage ratio compared to mice treated with Fc fragment (Fig. 4B).

DISCUSSION

Retinal ischemia is the underlying cause of retinal neovascularization. Since VEGF and VEGFR1 are upregulated in ischemic tissue (Forsythe et al., 1996; Gerber et al., 1997; Iyer et al., 1998), it is not surprising that VEGF plays a central role in the pathogenesis of retinal neovascularization. The pathogenesis of choroidal neovascularization is poorly understood. Choroidal blood flow is decreased in patients with AMD (Grunwald et al., 1998; Ross and Barofsky, 1998), but it is not known if this is sufficient to cause hypoxia. Also, it is unlikely that hypoxia is present in other disease processes, such as ocular histoplasmosis or degenerative myopia, in which choroidal neovascularization occurs in young patients. Since ischemia has not been implicated in the pathogenesis of choroidal neovascularization, this piece of evidence that made VEGF a prime suspect for retinal neovascularization is lacking for choroidal neovascularization. On the other hand, surgically removed choroidal neovascular membranes show immunohistochemical staining for VEGF (Amin et al., 1994; Frank et al., 1996; Kvanta et al., 1996; Lopez et al., 1996) and there is increased VEGF mRNA in experimentally induced choroidal neovascularization (Ogata

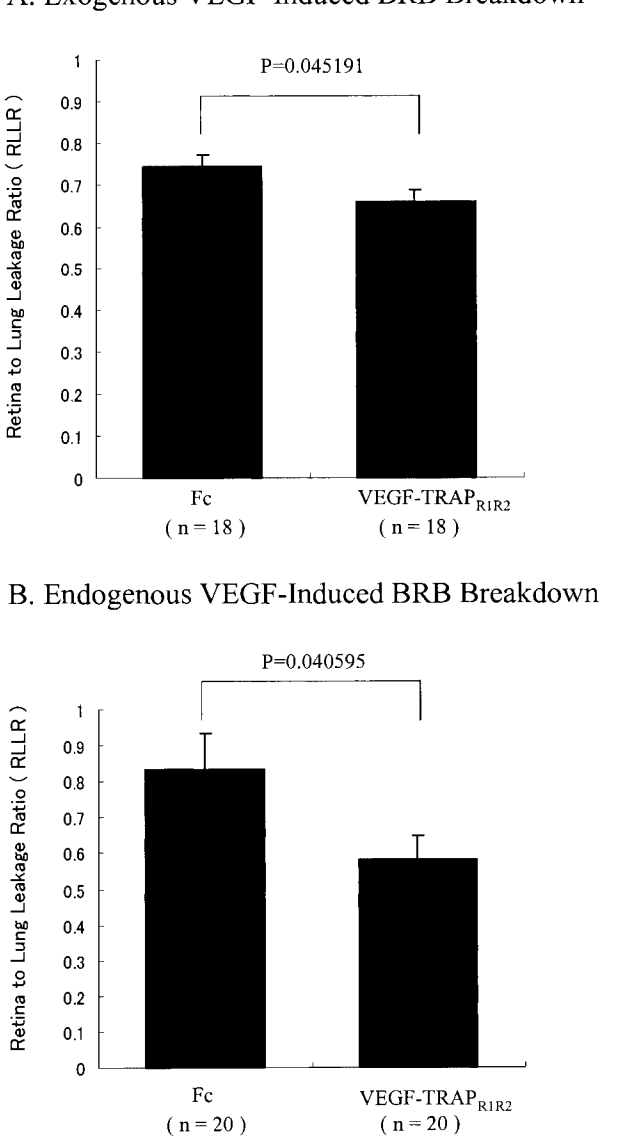

Fig. 4. Subcutaneous injections of VEGF-TRAP$_{R1R2}$ suppress VEGF-induced breakdown of the BRB. Adult C57BL/6 mice were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and on the following day received an intravitreous injection of 1 μg of 10^{-6} M VEGF. Six hours later, retinal vascular permeability was measured using [^{3}H]mannitol as a tracer. Mice treated with VEGF-TRAP$_{R1R2}$ (9 mice, 18 eyes) had a significantly smaller retina to lung leakage ratio (RLLR) than mice treated with Fc fragment (9 mice, 18 eyes) indicating less breakdown of the BRB (**A**). Double transgenic rtTA/rho-TRE/VEGF mice with doxycycline-inducible expression of VEGF in the retina were given a subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ (10 mice, 20 eyes) or Fc fragment (10 mice, 20 eyes) and on the following day they were started on 2 mg/ml of doxycycline in their drinking water. Two days later, they were given a second subcutaneous injection of 25 mg/kg of VEGF-TRAP$_{R1R2}$ or Fc fragment and then the next day retinal vascular permeability was measured with [^{3}H]mannitol as described in Materials and Methods. Double transgenic mice treated with VEGF-TRAP$_{R1R2}$ had a significant reduction in the retina to lung leakage ratio compared to mice treated with Fc fragment (**B**).

et al., 1996; Yi et al., 1997). Using a combination of kinase inhibitors, we previously demonstrated that VEGF signaling is necessary for development of choroidal neovascularization after laser-induced rupture of Bruch's membrane (Kwak et al., 2000). In the present study, using VEGF-TRAP$_{R1R2}$, a completely different type of VEGF inhibitor that is highly specific, we have confirmed that VEGF plays a prominent role in the development of choroidal neovascularization.

Systemic administration of VEGF-TRAP$_{R1R2}$ also markedly decreased neovascularization in rho/VEGF transgenic mice and reduced VEGF-induced breakdown of the BRB. Systemic administration of an earlier version of the VEGF-Trap also has been shown to reduce elevated ICAM-1 and eNOS levels, inhibit leukostasis, and normalize vascular permeability in the retinas of diabetic rodents (Qaum et al., 2001; Joussen et al., 2002; Poulaki et al., 2002). Thus, in model disease settings similar to diabetic retinopathy in humans, circulating VEGF-Traps penetrate into the retina and exert a strong therapeutic effect. The angiogenic stimulus is sustained in rho/VEGF mice, and subcutaneous injections of VEGF-TRAP$_{R1R2}$ every third day provided intraocular levels sufficient to neutralize this sustained stimulus. These data suggest that VEGF-TRAP$_{R1R2}$ deserves consideration as a potential treatment for two complications of diabetic retinopathy, retinal neovascularization and macular edema.

The effects of long-term systemic inhibition of VEGF are unknown. While there are theoretical reasons why this could be problematic, VEGF inhibitors have been tested as adjuncts to chemotherapy in cancer trials, and there have not been reports of severe problems clearly linked to blockade of VEGF. Should systemic inhibition of VEGF prove problematic, there is an alternative, because we have shown that, as is the case for other anti-VEGF approaches (EyeTech Study Group, 2002; Kryzstolik et al., 2002), local administration of VEGF-TRAP$_{R1R2}$ by intravitreous injection is a viable alternative. A single intravitreous injection of VEGF-TRAP$_{R1R2}$ markedly suppressed the development of choroidal neovascularization over the course of two weeks.

This study suggests that VEGF-TRAP$_{R1R2}$ has potential as a therapeutic agent for several VEGF-related retinal and choroidal diseases. Clinical trials are needed to assess the effect of subcutaneously administered VEGF-TRAP$_{R1R2}$ in patients with retinal neovascularization and/or macular edema due to ischemic retinopathies including diabetic retinopathy and retinal vein occlusions, and in patients with choroidal neovascularization. Concurrently, additional preclinical studies should explore modes of local delivery to the eye that can be used adjunctively or as an alternative to systemic administration.

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ARVO Annual Meeting Abstract | December 2002

Anti-Angiogenic Properties of a New VEGF Antagonist, VEGF Trap, in a Mouse Model of Retinal Neovascularization

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Abstract

Abstract: : **Purpose:** Excessive upregulation of VEGF expression appears to be responsible for pathologic neovascularization in many retinal diseases. We have developed a new VEGF antagonist, VEGF Trap, that binds VEGF with high affinity thereby neutralizing its action. The current study investigates the anti-angiogenic properties of VEGF Trap in a mouse model of oxygen-induced retinopathy (OIR). **Method:** OIR mice were produced following the method developed by Smith et al (IOVS 1994, 35:101-111). VEGF Trap (25mg/kg body weight) was administered by intraperitoneal (ip) injection every other day from PN13 (12-24 hours after returning the mice from hyperoxia to room air) to PN17. Littermates exposed to the same regimen of hyperoxia, received ip injections of 50 µl of PBS upon to room air and served as controls. Eyes were taken on PN19, and one retina was flat mounted and stained with fluorescent *Griffonia simplicifolia* lectin B4 to visualize the retinal vasculature. The contralateral eye was embedded, sectioned and stained with hematoxylin and eosin. **Results:** One week following return to room air (PN19), the retinas of all control mice exposed to hyperoxia exhibited marked pathologic angiogenesis, characterized by the presence of vascular tufts penetrating the inner limiting membrane and chaotic sprouting of vessels on the surface of the retina. Administration of VEGF Trap almost completely blocked the development of these vascular abnormalities. Although pathologic angiogenesis was dramatically inhibited, administration of the VEGF trap did not block all retinal angiogenesis. Remarkably, by PN 19 much of the central retina was appropriately revascularized in animals treated with VEGF Trap, as evidenced by the regrowth of normal appearing vessels in the superficial, intermediate and deep layers. **Conclusion:** Systemic administration of VEGF Trap can efficiently suppress pathologic retinal angiogenesis

without blocking the appropriate revascularization of the previously ischemic retina. This finding distinguishes the anti-angiogenic properties of VEGF Trap from many other angiogenesis inhibitors studied in this model, which appear to be either substantially less effective in blocking pathologic angiogenesis (Aiello LP et al. PNAS 1995, 92:10457-10461), or which also compromise the appropriate revascularization of the retina (Ozaki et al. Am J Pathol 1997, 156:697-707).

Keywords: 566 retinal neovascularization • 423 growth factors/growth factor receptors

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON10
	Confirmation No.	5070
	First Named Inventor	George D. Yancopoulos
	Application Number	17/352,892
	Filing Date	June 21, 2021
	Group Art Unit	To Be Assigned
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	To Be Assigned
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicant submits herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and copies of the foreign patents and non-patent literature are also enclosed.

The publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above-referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 3 September 2021

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10	5070

96387 7590 10/01/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
10/01/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/352,892	**Applicant(s)** YANCOPOULOS, George	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 21 June 2021 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10

CONFIRMATION NO. 5070

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

PUBLICATION NOTICE

OC00000128958842

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

Publication No.US-2021-0308217-A1
Publication Date:10/07/2021

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Oct 08, 2021 04:59:58 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17352892	NTC.PUB	10/07/2021	REGN-008CIPCON10

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10	5070

96387 7590 10/28/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
10/28/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Office Action Summary	Application No. 17/352,892	Applicant(s) YANCOPOULOS, George	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 21 June 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 21 June 2021 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed on 21 June 2021 has been entered in full. Claims 1-20 have been cancelled, and claims 21-50 have been added. Therefore, claims 21-50 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed 21 June 2021, 09 July 2021 and 03 September 2021 have been considered by the examiner.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van*

Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

5. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

6. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

7. Claims 21-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,254,338. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept

comprises. While the '338 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

8. Claims 21-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,669,069. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '069 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept comprises. While the '069 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

9. Claims 21-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 10,130,681. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the '681 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (VEGFR1) and Ig domain 3 of a second VEGF receptor (VEGFR2) and a multimerizing component, which is what aflibercept comprises. While the '681 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

10. Claims 21-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 10,828,345. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-11 of the '345 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a VEGF antagonist, wherein the VEGF comprises

an immunoglobin-like (Ig) domain 2 of Flt1 and Ig domain 3 of Flk1 and a multimerizing component, or aflibercept. While the '345 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

11. Claims 21-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 10,888,601. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-47 of the '601 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering aflibercept. While the '601 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

Summary

12. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon M. Lockard whose telephone number is (571) 272-2717. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama, can be reached on (571) 272-2911. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
October 22, 2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		10/23/2021	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	10/23/2021	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	10/23/2021	JML
PALM: Inventor search.	10/23/2021	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9,181	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 15:56
L2	1,053	l1 same ((chimer$ or fusion) same vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 15:56
L3	8,958	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 15:56
L4	536	l3 with ((chimer$ or fusion) with vegf)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 15:56
L5	6,443	aflibercept zaltrap eylea	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 15:58
L6	292	(l2 l4 l5) same ((eye or ocular or retina$ or macular) with disorder)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:00
L7	0	l6 and @pd<="2013"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:01
L8	14	l6 and @py<="2013"	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:02
L9	534	yancopoulos-g$.in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:03
L10	81	(l2 l4 l5) and l9	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:03
L11	35	l10 and (treat treating treatment).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/10/23 16:06

10/23/2021 4:07:10 PM
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	2021-06-21
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon Lockard
Sheet	1	of	18	Attorney Docket Number	REGN-008CIPCON10

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	7303746	2007-12-04	Wiegand	
	3	7303748	2007-12-04	Wiegand	
	4	7306799	2007-12-11	Wiegand	
	5	7396664	2008-07-08	Daly et al.	
	6	8092803	2012-01-10	Furfine et al.	
	7	9254338	2016-02-09	Yancopoulos	
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	117	Regeneron SEC Form 10-K (February 26, 2009)		
	118	Regeneron SEC Form 10-K (February 17, 2011)		
	119	Regeneron SEC Form 10-Q (May 8, 2006)		
	120	Regeneron SEC Form 10-Q (August 8, 2006)		

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	128	Regeneron SEC Form 10-Q (October 28, 2010)		
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	133	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)		
	134	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)		
	135	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)		
	136	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)		
	137	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)		
	138	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)		
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	140	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)		
	141	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)		
	142	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)		
	143	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)		
	144	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME) dated December 20, 2010." (December 20, 2010)		

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	145	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)		
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	161	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)		

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	205	SLAKTER et al., "A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) Outcomes at 1 Year" ARVO Annual Meeting Abstract (April 2009)		
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	210	STEWART, "Aflibercept" Nature Reviews: Drug Discovery 11:269-270 (04/01/2012)		

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	211	TANNOCK et al., "Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomized trial" Lancet Oncol (2013) 14:760-768		
	212	THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)		
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	214	THURSTON, "Vascular endothelial growth factor and other signaling pathways in developmental and pathologic angiogenesis." International Journal of Hematology, 80:7-20 (2004)		
	215	Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 38 pages, Latest version submitted October 27, 2014 on ClinicalTrials.gov (NCT01012973_01182013_27424.1)		
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	To Be Assigned
				Filing Date	2021-06-21
				First Named Inventor	George D. Yancopoulos
				Art Unit	
				Examiner Name	
Sheet	16	of	18	Attorney Docket Number	REGN-008CIPCON10

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Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
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				Filing Date	2021-06-21
				First Named Inventor	George D. Yancopoulos
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				Examiner Name	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/352,892
				Filing Date	2021-06-21
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	~~To Be Assigned~~ 1647
				Examiner Name	~~To Be Assigned~~ Jon Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON10

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Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	3	IPR2021-00880, Exhibit 1002, Albini Declaration (May 4, 2021)		
	4	IPR2021-00880, Exhibit 1003, Gerritsen Declaration (April 30, 2021)		
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/352,892
				Filing Date	2021-06-21
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	To Be Assigned
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FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 17:09:32 ON 23 OCT 2021

L1 533 S ((FLT1 OR VEGFR1) (S) (FLK1 OR KDR OR VEGFR2) (S) (FLT4 OR V
L2 1 S L1 (S) ((CHIMER? OR FUSION) (S) VEGF)
L3 9 S L1 (P) ((CHIMER? OR FUSION) (P) VEGF)
L4 1 S L1 (S) (CHIMER? OR FUSION)
L5 10 S L1 (P) (CHIMER? OR FUSION)
L6 14 S L1 AND (CHIMER? OR FUSION)
L7 15909 S AFLIBERCEPT OR ZALTRAP OR EYLEA
L8 9429 S (L1 OR L7) (P) (EYE OR OCCULAR OR RETINA? OR MACULAR)
L9 95 S (L1 OR L7) (P) ((EYE OR OCCULAR OR RETINA? OR MACULAR) (S
L10 53 DUP REM L9 (42 DUPLICATES REMOVED)
E YANCOPOULOS G/AU
L11 2394 S E3 OR E4 OR E6-E9
L12 63 S (L1 OR L7) AND L11
L13 25 DUP REM L12 (38 DUPLICATES REMOVED)

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CONFIRMATION NO. 5070

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
17/352,892	06/21/2021	424	1647	REGN-008CIPCON10

APPLICANTS

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

INVENTORS

George YANCOPOULOS, Yorktown Heights, NY;

**** CONTINUING DATA ***************************

This application is a CON of 17/350,958 06/17/2021
which is a CON of 17/112,404 12/04/2020
which is a CON of 17/072,417 10/16/2020
which is a CON of 16/055,847 08/06/2018 PAT 10857205
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and claims benefit of 61/561,957 11/21/2011

**** FOREIGN APPLICATIONS ***************************

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07/01/2021

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	1	30	4

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Regeneron - Bozicevic, Field & Francis
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REDWOOD CITY, CA 94065
UNITED STATES

TITLE

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	☐ All Fees
3300	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)

		❑ Other _____
		❑ Credit

Inventor Information for 17/352892

/J.L./

Inventor Name	City	State/Country
YANCOPOULOS, GEORGE	YORKTOWN HEIGHTS	NEW YORK

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Grz

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	June 21, 2021	

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	June 21, 2021	

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	25	Bashshur *et al.*, "Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration" Am J. Ophthalmology 142: 1 (2006)	Herewith
	26	Bayer Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." May 8, 2008	Herewith
	27	Bayer Press Release, "VEGF Trap-Eye Shows Positive Results in Phase II Study in Patients with Diabetic Macular Edema" February 18, 2010	Herewith
	28	Bayer Press Release, "Bayer HealthCare and Regeneron Announce Encouraging 32-Week Follow Up Results From A Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration" April 28, 2008	Herewith
	29	Bayer Press Release "Bayer HealthCare and Regeneron Announce VEGF Trap-Eye Achieved Durable Improvement in Vision Over 52 Weeks in a Phase 2 Study in Patients with Age-Related Macular Degeneration" August 19, 2008	Herewith

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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	Regeneron Pharmaceuticals, Inc.	
	FILING DATE	GROUP
	June 21, 2021	

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	30	BMJ Publishing Group Ltd., "Review: Ranibizumab (Lucentis) In Neovascular Age-Related Macular Degeneration: Evidence From Clinical Trials" British J. Ophthalmology (December 2020), https://bjo.bmj.com/content/94/1/2.altmetrics	Herewith
	31	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals" Drugs and the Pharmaceutical Sciences 85:91-108 (1997)	Herewith
	32	Bressler, N. M. and G. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study, "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2." Arch Ophthalmol 119(2): 198-207 (2001)	Herewith
	33	Brown & Regillo, "Anti-VEGF Agents in the Treatment of Neovascular Age-Related Macular Degeneration: Applying Clinical Trial Results to the Treatment of Everyday Patients" Am J. Ophthalmology 144: 627 (2007)	Herewith
	34	Chi *et al.*, "Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation" Pharmaceutical Research Vol. 20, No. 9, 1325-1336 (September 2003)	Herewith
	35	Ciulla & Rosenfeld, "Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration" Current Opinion Ophthalmology 20: 158 (2009)	Herewith
	36	Clinicaltrials.gov. I-SPY 2 TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer, Accessed 2010; http://clinical trials.gov/ct2/show/NCT01042379?term-NCT01042379&rank=1	Herewith
	37	CMS, Local Coverage Determination (LCD) for Ranibizumab (Lucentis) (L29266, First Coast Service Options, Inc June 14, 2011)	Herewith
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	39	Department of Health and Human Services, Office of Inspector General, "Questionable Billing for Medicare Ophthalmology Services" September 2015 OEI-04-12-00280	Herewith
	40	Drug Vehicle (Code C927), National Cancer Institute (NCI). Retrieved January 6, 2021, from https://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary =NCI_Thesaurus&code=C927&ns=ncit	Herewith

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		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	41	EP 2 663 325 File History	Herewith
	42	Eylea® Prescribing Information, Revised 05/2019	Herewith
	43	Ferrara, N. & Kerbel, R., "Angiogenesis as a Therapeutic Target" Nature 438: 967 (2005)	Herewith
	44	Fraser *et al.*, "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function." J. Clin. Endocrinol & Metab. 90(2): 1114-1122 (February 2005)	Herewith
	45	Genentech, "FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration," News Release dated June 30, 2006 (June 30, 2006)	Herewith
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	47	Heier, "Intravitreal VEGF Trap for AMD: An Update" Retina Today 44 (October 2009)	Herewith
	48	Heier, J. S., P. A. Campochiaro, L. Yau, Z. Li, N. Saroj, R. G. Rubio and P. Lai "Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial" Ophthalmology 119(4): 802-809 (2012)	Herewith
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	51	Ip, M. S., I. U. Scott, P. C. VanVeldhuisen, N. L. Oden, B. A. Blodi, M. Fisher, L. J. Singerman, M. Tolentino, C. K. Chan, V. H. Gonzalez and S. S. R. Group "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5" Arch Ophthalmol 127(9): 1101-1114 (2009)	Herewith
	52	Janeway *et al.*, "The structure of a typical antibody molecule" Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science (2001)	Herewith
	53	Keane *et al.*, "Effect of Ranibizumab Retreatment Frequency on Neurosensory Retinal Volume in Neovascular AMD" Retina 29: 592 (2009)	Herewith
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	69	Regeneron Pharmaceuticals Inc. Regeneron Reports Fourth Quarter and Full Year 2005 Financial and Operating Results. Media Release: 24 Feb 2006. Available from URL: http://regeneron.com	Herewith
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		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
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	86	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., "Age-Related Macular Degeneration: What You Should Know" (Sept. 2015) https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf	Herewith
	87	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., "Diabetic Retinopathy: What You Should Know" (Sept. 2015), https://www.nei.nih.gov/sites/default/files/2019-06/Diabetic-Retinopathy-What-You-Should-Know-508.pdf	Herewith
	88	U.S. Department of Health and Human Services Food and Drug Administration, "Guidance for industry Q1A(R2) stability testing of new drug substances and products" Rockville, MD (November 2003)	Herewith
	89	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 ("NCT-795")	Herewith
	90	Wall Street Journal, "Genentech's Big Drug for Eyes Faces a Rival" (2007)	Herewith
	91	Wulff *et al.,* "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" Endocrinology 143(7): 2797-2807 (July 2002)	Herewith
	92	XOLAIR® label	Herewith
	93	Zarbin & Rosenfeld, "Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives" Retina 30: 1350 (2010)	Herewith

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/JON M LOCKARD/	10/22/2021

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From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Oct 28, 2021 03:59:18 AM

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Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
17352892	CTNF	10/28/2021	REGN-008CIPCON10
	1449	10/28/2021	REGN-008CIPCON10
	1449	10/28/2021	REGN-008CIPCON10
	1449	10/28/2021	REGN-008CIPCON10

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Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1.	US 2004/0213787 A1	2004-10-28	Sleeman *et al.*	not required per 69 Fed. Reg. 56481
	2.	US 6,833,349 B2	2004-12-21	Xia *et al.*	not required per 69 Fed. Reg. 56481
	3.	US 2004/0266688 A1	2004-12-30	Nayak	not required per 69 Fed. Reg. 56481
	4.	US 2005/0032699 A1	2005-02-10	Holash *et al.*	not required per 69 Fed. Reg. 56481
	5.	US 6,879,294 B2	2005-05-24	Davis-Smyth *et al.*	not required per 69 Fed. Reg. 56481
	6.	US 2005/0281822 A1	2005-12-22	Cedarbaum *et al.*	not required per 69 Fed. Reg. 56481
	7.	US 2006/0030000 A1	2006-02-09	Alitalo *et al.*	not required per 69 Fed. Reg. 56481
	8.	US 7,378,095 B2	2008-05-27	Cao *et al.*	not required per 69 Fed. Reg. 56481
	9.	US 7,482,002 B2	2009-01-27	Cedarbaum	not required per 69 Fed. Reg. 56481
	10.	US 2009/0264358 A1	2009-10-22	Yu	not required per 69 Fed. Reg. 56481
	11.	US 7,750,138 B2	2010-07-06	Fang *et al.*	not required per 69 Fed. Reg. 56481
	12.	US 7,951,585 B2	2011-05-31	Ke	not required per 69 Fed. Reg. 56481
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		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	16.	CN 1304427C	2007-03-14	China	Machine translation	Previously in US Application 17/072,417
	17.	CN 100502945C	2009-06-24	China	Corresponds to US 2009/0264358 A1	Previously in US Application 17/072,417
	18.	CN 100567325C	2009-12-09	China	Machine translation	Previously in US Application 17/072,417
	19.	WO 2012/097019	2012-07-19	WIPO	N/A	Previously in US Application 17/072,417
	20.	CN 102233132 B	2013-10-23	China	Machine translation	Previously in US Application 17/072,417

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	21.	CN 102380096 B	2014-04-30	China	Machine translation	Previously in US Application 17/072,417
	22.	CN 103212075 B	2017-06-27	China	Machine translation	Previously in US Application 17/072,417
	23.	CN 107115294 A	2017-09-01	China	Machine translation	Previously in US Application 17/072,417

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	24.	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	25.	Anonymous, Meeting Archive Titled "PA040 One-Year Results of the DA VINCI Study of VEGF Trap-Eye in Diabetic Macular Edema," presented by Diana V Do, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417
	26.	Anonymous, Meeting Archive Titled "PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration," presented by David S Boyer, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	27.	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	28.	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	29.	Anonymous, Meeting Archive Titled "PO492 One-Year Results of the VIEW 1 and VIEW 2 Studies: VEGF Trap-Eye in Wet AMD," presented by David M Brown MD at Orange County Center (October 2011)	Previously in US Application 17/072,417
	30.	Anonymous, Meeting Archive Titled "PO549 The 6-Month (Primary Endpoint) Results of the Phase 3 GALILEO Study: VEGF Trap-Eye in Central Retinal Vein Occlusion," presented by Jean-Francois Korobelnik, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417

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	34.	Brown *et al.*, "Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6647 *(April 2011)*	Previously in US Application 17/072,417
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	37.	Center for Drug Evaluation and Research Application Number: 21-756 Medical Review(s) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	Previously in US Application 17/072,417
	38.	Center for Drug Evaluation and Research BLA Application Number: 125156 Medical Review, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_MedR.pdf>	Previously in US Application 17/072,417
	39.	Cheung *et al.*, "Combined anti-PIGF and anti-VEGF Therapy Ameliorates Pathological Neovascularization and Improves Retinal Revascularization in the Murine Model of Oxygen Induced Ischemic Retinopathy," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6064 (April 2011)	Previously in US Application 17/072,417
	40.	Dixon *et al.*, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," *Expert Opin. Investig. Drugs*, 18(10):1573-1580 (2009)	Previously in US Application 17/072,417

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	47.	Kaiser, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema," *Br. J. Ophthalmol.*, 93(2):135-36 (February 2009)	Previously in US Application 17/072,417
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	52.	Lucentis Approval (June 30, 2006)	Previously in US Application 17/072,417
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	57.	Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration," *Biodrugs*, 24(3):183-194 (2010)	Previously in US Application 17/072,417
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	61.	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	62.	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
	63.	Regeneron Pharmaceuticals Inc., "Regeneron Reports First Quarter 2008 Financial and Operating Results," Press release May 1, 2008.	Previously in US Application 17/072,417
	64.	Regeneron Pharmaceuticals Inc., Form 10-Q, published November 7, 2007, for the period ending September 30, 2007.	Previously in US Application 17/072,417

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	66.	Rosenfeld *et al.*, "Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration," *Ophthalmic. Surg. Lasers Imaging*, 36(4):331-335 (2005)	Previously in US Application 17/072,417
	67.	Scott *et al.*, "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6," *Arch. Ophthalmol.*, 127(9):1115-1128 & 127(12):1653 (2009)	Previously in US Application 17/072,417
	68.	Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy," *Diabetes Care*, 32(8):1556-1562 (August 2009)	Previously in US Application 17/072,417
	69.	Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results," September 28, 2008.	Previously in US Application 17/072,417
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	73.	IPR2021-00880 dated November 10, 2021, for US 9,669,069 B2	Previously in US Application 17/072,417
	74.	IPR2021-00881 dated November 10, 2021, for US 9,254,338 B2	Previously in US Application 17/072,417

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	87.	Bayer Press Release, "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration," May 8, 2008	Previously in US Application 17/072,417
	88.	Bayer Press Release, "Bayer HealthCare and Regeneron Announce Encouraging 32-Week Follow Up Results From A Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration," April 28, 2008	Previously in US Application 17/072,417

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	108.	Information from ClinicalTrials.gov archive on the VIEW 1 study (NCT00509795) "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1)," changes from v8 (March 3, 2009) to v9 (April 28, 2009)	Previously in US Application 17/072,417
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	111.	Kim *et al.*, "Potent VEGF Blockade Causes Regression of Coopted Vessels in a Model of Neuroblastoma," *Proc. Nat'l Acad. Sci.*, 99(17):11399-11404 (2002)	Previously in US Application 17/072,417
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SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

NON-PATENT LITERATURE DOCUMENTS - UPDATES TO PREVIOUS IDS CITATIONS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	118.	Phosphate buffer. Cold Spring Harbor Protocols 2006: pdb.rec8543 (2006)	Previously in US Application 17/072,417
	119.	Randolph & Jones, "Surfactant-Protein Interactions" *Rational Design of Stable Protein Formulations* pp. 159-175, Springer, Boston, MA (2002)	Previously in US Application 17/072,417
	120.	Raptiva Label (Final Labelling 03-13-2009)	Previously in US Application 17/072,417
	121.	Regeneron Pharmaceuticals Inc., Regeneron Reports Fourth Quarter and Full Year 2004 Financial and Operating Results. Media Release: 22 Feb 2005.	Previously in US Application 17/072,417
	122.	Regeneron Pharmaceuticals Inc., Regeneron Reports Fourth Quarter and Full Year 2005 Financial and Operating Results. Media Release: 24 Feb 2006.	Previously in US Application 17/072,417
	123.	Regeneron Pharmaceuticals Inc., Regeneron Reports Positive Phase 1 Data for the VEGF Trap in Age-Related Macular Degeneration; Preliminary Results Show Improvements in Vision and Reginal Swelling; VEGF Trap Was Well Tolerated at All Dose Levels. Media Release: 1 May 2006.	Previously in US Application 17/072,417
	124.	Regeneron SEC Form 10-Q (September 30, 2009)	Previously in US Application 17/072,417
	125.	Reichert, "Antibody-Based Therapeutics To Watch In 2011," *MABS*, 3(1):76-99 (2011)	Previously in US Application 17/072,417
	126.	Remicade Label (Revised November 2013)	Previously in US Application 17/072,417
	127.	Retina Coding Q & A, Retinal Physician, 16: 18, 54 (July/August 2019)	Previously in US Application 17/072,417
	128.	Rogers *et al.*, "The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia," *Ophthalmology*, 117(2):313-319e1 (2010)	Previously in US Application 17/072,417
	129.	Rudge *et al.*, "VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene-based Discovery of the Next Generation of Angiogenesis Targets," *Cold Spring Harbor Symposia on Quantitative Biology*, 70:411-418 (2005)	Previously in US Application 17/072,417
	130.	Schmidt-Erfurth, "Current Concepts in the Management of Diabetic Macular Edema," *Johns Hopkins Advanced Studies in Ophthalmology*, 7(2):52-59 (2010)	Previously in US Application 17/072,417
	131.	Simulect Label (May 1998)	Previously in US Application 17/072,417
	132.	Spaide *et al.*, "Prospective Study of Intravitreal Ranibizumab as a Treatment for Decreased Visual Acuity Secondary to Central Retinal Vein Occlusion," *Am. J. Ophthalmology*, 147(2):298-306 (2009)	Previously in US Application 17/072,417
	133.	Spielberg, L. & Leys, A., "Intravitreal Bevacizumab for Myopic Choroidal Neovascularization: Short-Term and 1-Year Results," *Bulletin Societe Belge D'Ophtalmologie*, 312:17-27 (2009)	Previously in US Application 17/072,417

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

NON-PATENT LITERATURE DOCUMENTS - UPDATES TO PREVIOUS IDS CITATIONS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	134.	Steinbrook, "The Price of Sight — Ranibizumab, Bevacizumab, and the Treatment of Macular Degeneration," *N. Eng. J. Med.*, 355(14):1409-1412 (2006)	Previously in US Application 17/072,417
	135.	The Branch Vein Occlusion Study, G., "Argon laser photocoagulation for macular edema in branch vein occlusion," *Am. J. Ophthalmology*, 98(3):271-282 (1984)	Previously in US Application 17/072,417
	136.	The Central Vein Occlusion Study, G., "Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report," *Ophthalmology*, 102(10):1425-1433 (1995)	Previously in US Application 17/072,417
	137.	U.S. Department of Health and Human Services, Food and Drug Administration, "Guidance for industry Q1A(R2) stability testing of new drug substances and products," Rockville, MD (November 2003)	Previously in US Application 17/072,417
	138.	U.S. Department of Health and Human Services, National Institute of Health, National Eye Institute, "Age-Related Macular Degeneration: What You Should Know," (Sept. 2015) https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf	Previously in US Application 17/072,417
	139.	U.S. Department of Health and Human Services, National Institute of Health, National Eye Institute, "Diabetic Retinopathy: What You Should Know," (Sept. 2015) https://www.nei.nih.gov/sites/default/files/2019-06/Diabetic-Retinopathy-What-You-Should-Know-508.pdf	Previously in US Application 17/072,417
	140.	U.S. Department of Health and Human Services, Office of Inspector General, "Questionable Billing for Medicare Ophthalmology Services" September 2015 OEI-04-12-00280	Previously in US Application 17/072,417
	141.	Wall Street Journal, "Genentech's Big Drug for Eyes Faces a Rival" (2007)	Previously in US Application 17/072,417
	142.	Wulff *et al.*, "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" Endocrinology 143(7): 2797-2807 (July 2002)	Previously in US Application 17/072,417
	143.	Xolair Label (2003)	Previously in US Application 17/072,417
	144.	Zarbin & Rosenfeld, "Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives" Retina 30: 1350 (2010)	Previously in US Application 17/072,417

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

*Copies of the listed references are either submitted herewith or were previously cited by or submitted to, the Office in a prior application. Pursuant to 37 C.F.R. § 1.97(d) and MPEP §609, the indicated reference may have been previously cited by or submitted to, the Office in a prior application, where the prior application is identified by its U.S. Application Number in this Information Disclosure Statement.

Electronic Patent Application Fee Transmittal

Application Number:	17352892
Filing Date:	21-Jun-2021
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	44366548
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	24-NOV-2021
Filing Date:	21-JUN-2021
Time Stamp:	14:56:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E2021ANE57083518
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON10_2021-11-24_SuppIDS_Trans.pdf	52936 162b8919da83cc173675eac4fd63bd0dac904188	no	3
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON10_2021-11-24_SuppIDS_1449.pdf	126841 bbe2331eadef194d51c7ba0712d7eac5a71630e4	no	12
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	38441 a2d655de99184cafbef2b0636cb686d73cc36255	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	218218		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON10
	Confirmation No.	5070
	First Named Inventor	George D. Yancopoulos
	Application Number	17/352,892
	Filing Date	June 21, 2021
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

The attention of the Examiner is invited to the documents listed on the attached Substitute 1449.

Copies of the U.S. patents and published applications listed on the attached Substitute 1449 are not submitted herewith, in accordance with the Strategic Plan Final Rule, 69 Fed. Reg. 56481-56547 (September 21, 2004), effective October 21, 2004.

Copies of the foreign publications and non-patent literature documents listed on the attached Substitute 1449 are submitted in parent U.S. Application No. 17/072,417. Applicant respectfully submits that a subset of references submitted herein were previously submitted in this or a priority application. Nonetheless, Applicant is submitting these previously submitted references to provide an accurate reference citation or to provide a clearer copy of the reference.

Applicant notes that the transmittal letter accompanying the Information Disclosure Statement submitted for this application on July 9, 2021, incorrectly recited that "[a]ll of the references identified herein were disclosed in parent application serial number 17/350,958." Accordingly, the citations previously submitted in the July 9, 2021 Information Disclosure Statement are resubmitted here as Ref. Nos. 75 to 143 in order to correct the record. Applicant notes that this group of resubmitted citations accounts for part of the citations provided herein.

Applicant would also like to bring to the Examiner's attention that the PTAB has instituted *inter partes* reviews for related U.S. Patent Nos. 9,254,338 and 9,669,069.

It is respectfully requested that the information above be expressly considered during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

No aspect of these submissions constitute admission of prior art status or a disclaimer of claim scope.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above-referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 24 November 2021

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
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Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
17/352,892	June 21, 2021

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 96387

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Frank R. Cottingham/	Date (Optional)	
Name	Frank R. Cottingham		
Title	Executive Director, Assistant General Counsel, Patents, Regeneron Pharmaceuticals, Inc.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 17/352,892 Filed/Issue Date: June 21, 2021

Titled: Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

Regeneron Pharmaceuticals, Inc., a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 057417, Frame 0322, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Karl Bozicevic, Reg. No. 28,807/	29 November 2021
Signature	Date
Karl Bozicevic	28,807
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	44381316
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	29-NOV-2021
Filing Date:	21-JUN-2021
Time Stamp:	14:43:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	0725US11_POA.pdf	168264 d9241ecc281e761ddacaf4a3cfdacf0b953644ac	no	1

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	REGN-008CIPCON10_2021-11-29_aia0096.pdf	118254 a08dd5739cc2bcc90980d78bb574ba82d4026f3a	no	3
Warnings:					
Information:					
			Total Files Size (in bytes):	286518	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10

CONFIRMATION NO. 5070

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

POA ACCEPTANCE LETTER

OC000000130128563

Date Mailed: 12/01/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/29/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Dec 01, 2021 04:06:38 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
17352892	N570	12/01/2021	REGN-008CIPCON10

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Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Electronically filed		
REPLY UNDER 37 C.F.R. §1.111	Attorney Docket No.	REGN-008CIPCON10
	Confirmation No.	5070
	First Named Inventor	George D. Yancopoulos
	Application Number	17/352,892
	Filing Date	June 21, 2021
Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1647
	Examiner Name	Lockard, Jon McClelland
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

This reply is responsive to the Office Action dated October 28, 2021, for which a three-month period for response was given, making this response due on January 28, 2022. Accordingly, this response is timely filed.

In view of the attached Terminal Disclaimer and the remarks put forth below, reconsideration and allowance are respectfully requested.

Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

CLAIMS

No amendment is being sought in this response. Claims are presented for the Examiner's convenience only.

1. - 20. (Canceled)

21. (Previously Presented) A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;

wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

22. (Previously Presented) The method of claim 21 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

23. (Previously Presented) The method of claim 22 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

24. (Previously Presented) The method of claim 23 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

25. (Previously Presented) The method of claim 23 wherein only two secondary doses are administered to the patient.

26. (Previously Presented) The method of claim 23 wherein the aflibercept is formulated as an isotonic solution.

27. (Previously Presented) The method of claim 23 wherein the aflibercept is formulated with a nonionic surfactant.

28. (Previously Presented) The method of claim 22 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

29. (Previously Presented) The method of claim 28 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

30. (Previously Presented) The method of claim 22 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

31. (Previously Presented) The method of claim 30 wherein only two secondary doses are administered to the patient.

32. (Previously Presented) The method of claim 30 wherein the aflibercept is formulated as an isotonic solution.

33. (Previously Presented) The method of claim 30 wherein the aflibercept is formulated with a nonionic surfactant.

34. (Previously Presented) The method of claim 21 wherein exclusion criteria for the patient include both of:

(1)active ocular inflammation; and

(2) active ocular or periocular infection.

35. (Previously Presented) A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

36. (Previously Presented) The method of claim 35 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

37. (Previously Presented) The method of claim 36 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

38. (Previously Presented) The method of claim 37 wherein the aflibercept is formulated as an isotonic solution.

39. (Previously Presented) The method of claim 37 wherein the aflibercept is formulated with a non- ionic surfactant.

40. (Previously Presented) The method of claim 37 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.

41. (Previously Presented) The method of claim 36 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

42. (Previously Presented) The method of claim 41 wherein the aflibercept is formulated as an isotonic solution.

43. (Previously Presented) The method of claim 41 wherein the aflibercept is formulated with a nonionic surfactant.

44. (Previously Presented) The method of claim 35 wherein only two secondary doses are administered to the patient.

45. (Previously Presented) The method of claim 35 wherein four secondary doses are administered to the patient.

46. (Previously Presented) A method of treating age related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

47. (Previously Presented) The method of claim 46 wherein only two secondary doses are administered to the patient.

48. (Previously Presented) The method of claim 46 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

49. (Previously Presented) A method of treating age-related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

50. (Previously Presented) The method of claim 49 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

REMARKS

Formal Matters

Claims 21-50 are pending.

Original claims 1-20 were canceled without prejudice.

No claims are amended.

No claims are added.

No New Matter is added.

Statement under 37 C.F.R. §§1.56 and 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent 9,254,338, for which *Inter Partes* Review No. IPR2021-00881 was filed on May 5, 2021, in which a trial was instituted on November 10, 2021.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 14/972,560, filed December 17, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069, for which *Inter Partes* Review No. IPR2021-00880 was filed on May 5, 2021, in which a trial was instituted on November 10, 2021.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 15/471,506, filed March 28, 2017 which issued on November 20, 2018 as U.S. Patent No. 10,130,681.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 16/055,847, filed August 6, 2018 which will issue on December 8, 2020 as U.S. Patent No. 10,857,205.

The Applicant wishes to bring to the Examiner's attention U.S. Patent Application No. 16/159,282, filed October 12, 2018 which issued on November 10, 2020 as U.S. Patent No. 10,828,345, for which Post-Grant Review No. PGR2021-00035 was filed on January 7, 2021, which is now terminated.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/397,267, filed April 29, 2019, which issued on January 12, 2021 as U.S. Patent No. 10,888,601.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 17/072,417, filed October 16, 2020 for which no actions have been mailed.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application 17/112,063, filed December 4, 2020 for which no actions have been mailed.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 17/112,404 filed December 4, 2020 for which no actions have been mailed.

The Applicant wishes to bring to the Examiner's attention co-pending U.S. Patent Application No. 17/350,958 filed June 17, 2021 for which no actions have been mailed.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

Non-statutory double patenting Rejections

Claims 21-50 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-26 of U.S. Patent No. 9,254,338.

Claims 21-50 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 9,669,069.

Claims 21-50 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 10,130,681.

Claims 21-50 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-11 of U.S. Patent No. 10,828,345.

Claims 21-50 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-47 of U.S. Patent No. 10,888,601.

Response

Solely to expedite prosecution and not in acquiescence to the Examiner's rejections, Applicant submits a Terminal Disclaimer herewith with regard to U.S. Patent Nos. 9,254,338; 9,669,069; 10,130,681; 10,828,345; and 10,888,601. Additionally, it is noted that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *See, e.g., Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, (Fed. Cir. 1991) (filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection); *Motionless Keyboard Co. v. Microsoft Corp.*, 486 F.3d 1376, 1385 (Fed. Cir. 2007) ("A terminal disclaimer is simply not an admission that a later-filed invention is obvious."); *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 941 (Fed. Cir. 1992) (holding that filing of terminal disclaimer did not serve as admission of obviousness-type double patenting). Because there are no other rejections outstanding, the application is believed to be in condition for allowance and an indication of such is respectfully requested.

CONCLUSION

Applicants submit that all the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 7 December 2021

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Attached: Terminal Disclaimer

PTO/SB/26 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) **REGN-008CIPCON10**

In re Application of: **Yancopoulos, George D.**

Application No.: **17/352,892**

Filed: **June 21, 2021**

For: **Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders**

The owner, **Regeneron Pharmaceuticals, Inc.**, of **100%** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** Nos. **9,254,338; 9,669,069; 10,130,681; 10,828,345; and 10,888,601;** as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patents** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patents**, "as the term of said **prior patents** is presently shortened by any terminal disclaimer," in the event that said **prior patents** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 28,807

/Karl Bozicevic, Reg. No. 28,807/ — Signature

7 December 2021 — Date

Karl Bozicevic, Reg. No. 28,807 — Typed or printed name

650-833-7735 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	17352892
Filing Date:	21-Jun-2021
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
		Total in USD ($)		**170**

Electronic Acknowledgement Receipt

EFS ID:	44456586
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	07-DEC-2021
Filing Date:	21-JUN-2021
Time Stamp:	17:20:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$170
RAM confirmation Number	E2021B7H21203029
Deposit Account	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-008CIPCON10_2021-12-07_Amendment.pdf	68698 ed2e5354535a93c33f95ba4806079d4e3062f321	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	10	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	REGN-008CIPCON10_2021-12-07_Terminal_Disclaimer_Prior_Pat.pdf	25017 530a143c5bc6a23282322d78b31137c9a5c0c584	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	38249 7fd79bad8ce4a26fd26ead8b1975d88a5592583e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	131964		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 17/352,892 *	17/352,892	YANCOPOULOS, George	
	Examiner	**Art Unit**	
	LOCKARD, JON MCCLELLAND	1647	

Document Code - DISQ	**Internal Document - DO NOT MAIL**

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: **07 December 2021**	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

/LAWANA R HIXON/

Technology Center: OPLC

Telephone: (571)272-6074

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/352,892	Filing Date 06/21/2021	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/07/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/352,892
				Filing Date	June 21, 2021
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON10

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6897294	2005-05-24	Davis-Smyth et al.	

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					

	NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1			

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	17352892
Filing Date:	21-Jun-2021
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	44540302
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	16-DEC-2021
Filing Date:	21-JUN-2021
Time Stamp:	17:36:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E2021BFH37171715
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-008CIPCON10_2021-12-16_SuppIDS_Trans.pdf	50042 3932d0d3aedccce743f7dd65adf48c2001d62041	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-008CIPCON10_2021-12-16_SuppIDS_SB08A.pdf	22187 d208a68d729acc2bbb65373a6a8ebc1211fbea29	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	38441 ef41e3f587ac020e1a8dd8cf5d2de0b4a8e239d9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	110670		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-008CIPCON10
	Confirmation No.	5070
	First Named Inventor	George D. Yancopoulos
	Application Number	17/352,892
	Filing Date	June 21, 2021
	Group Art Unit	1647
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jon McClelland Lockard
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Applicant submits herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A.

The publications discussed herein are provided to comply with the duty to disclose in accordance with 37 C.F.R. § 1.56. However, nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☐ No fee is believed to be due.

☒ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above-referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 16 December 2021

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 12/22/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/22/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10	5070

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/22/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

96387 7590 12/22/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10	5070

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/22/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	06/21/2021	George YANCOPOULOS	REGN-008CIPCON10	5070

96387 7590 12/22/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/22/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/352,892	Applicant(s) YANCOPOULOS, George	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Response filed 07 December 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-50 (renumbered as claims 1-30, respectively) . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Terminal Disclaimer

2. The terminal disclaimer filed on 07 December 2021 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 9,254,338**, **U.S. Patent No. 9,669,069**, **U.S. Patent No. 10,130,681, U.S. Patent No. 10,828,345** and **U.S. Patent No. 10,888,601** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 24 November 2021 and 16 December 2021 have been considered by the examiner.

Withdrawn Objections and/or Rejections

4. The rejection of claims 21-50 on the ground of nonstatutory obviousness-type double patenting as set forth at pp. 2-6 of the previous Office action (mailed 28 October 2021) is withdrawn in view of Applicant's submission of a terminal disclaimer (filed 07 December 2021).

Summary

5. Claims 21-50 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
December 16, 2021

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
A61K	/	38	/	179	F	2013-01-01
C07K	/	16	/	22	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	32	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	16 December 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	17 December 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20211215

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	38	/	17	
C07K	/	14	/	71	
C07K	/	19	/	00	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JON M LOCKARD/ Examiner, Art Unit 1647	16 December 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	17 December 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	**Art Unit**
	JON M LOCKARD	1647

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JON M LOCKARD/ Examiner, Art Unit 1647	16 December 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	17 December 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		10/23/2021	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	10/23/2021	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	10/23/2021	JML
PALM: Inventor search.	10/23/2021	JML

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/352,892	YANCOPOULOS, George
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	12/16/2021	JML
	PALM: Inventor search.	12/16/2021	JML
	IPR2021-00880 Reviewed Inter Partes Review of U.S. Patent No. 9,669,069.	12/16/2021	JML
	IPR2021-00881 Reviewed Inter Partes Review of U.S. Patent No. 9,254,338.	12/16/2021	JML
	IPR2021-00035 Reviewed Inter Partes Review of U.S. Patent No. 10,828,345.	12/16/2021	JML
	IPR2022-00257 Reviewed Inter Partes Review of U.S. Patent No. 9,669,069.	12/16/2021	JML
	IPR2022-00258 Reviewed Inter Partes Review of U.S. Patent No. 9,254,338.	12/16/2021	JML
	IPR2022-00298 Reviewed Inter Partes Review of U.S. Patent No. 9,254,338 B2.	12/16/2021	JML
	IPR2022-00301 Reviewed Inter Partes Review of U.S. Patent No. 9,669,069 B2.	12/16/2021	JML

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	17/352,892
				Filing Date	June 21, 2021
				First Named Inventor	George D. YANCOPOULOS
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	1	Attorney Docket Number	REGN-008CIPCON10

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.L/	1	6897294	2005-05-24	Davis-Smyth et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T
	1			

Examiner Signature	/JON M LOCKARD/	Date Considered	12/17/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

EAST Search History

EAST Search History (Interference)

/J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2,967	(flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	USPAT	OR	ON	2021/12/16 11:32
L2	301	l1 same ((chimer$ or fusion) same vegf)	USPAT	OR	ON	2021/12/16 11:32
L3	2,906	(flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3)))	USPAT	OR	ON	2021/12/16 11:32
L4	159	l3 with ((chimer$ or fusion) with vegf)	USPAT	OR	ON	2021/12/16 11:32
L5	1,906	aflibercept zaltrap eylea	USPAT	OR	ON	2021/12/16 11:33
L6	97	(l2 l4 l5) same ((eye or ocular or retina$ or macular) with disorder)	USPAT	OR	ON	2021/12/16 11:33
L7	3	l6 and @py<="2013"	USPAT	OR	ON	2021/12/16 11:33
L8	172	yancopoulos-g$.in.	USPAT	OR	ON	2021/12/16 11:33
L9	38	(l2 l4 l5) and "l9"	USPAT	OR	ON	2021/12/16 11:34
L10	32	(l2 l4 l5) and l8	USPAT	OR	ON	2021/12/16 11:34
L11	14	l10 and (treat treating treatment).clm.	USPAT	OR	ON	2021/12/16 11:34
L12	1,872	aflibercept zaltrap eylea.clm.	USPAT	OR	ON	2021/12/16 11:35
L13	86	l12 and ((eye or ocular or retina$ or macular) with disorder).clm.	USPAT	OR	ON	2021/12/16 11:35

12/16/2021 11:37:15 AM
C:\Users\jlockard\Documents\EAST\Workspaces\17352892.wsp

SUBSTITUTE 1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO.	APPLICATION NO.
	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

U.S. PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	NAME	REFERENCE PROVIDED*
	1.	US 2004/0213787 A1	2004-10-28	Sleeman *et al.*	not required per 69 Fed. Reg. 56481
	2.	US 6,833,349 B2	2004-12-21	Xia *et al.*	not required per 69 Fed. Reg. 56481
	3.	US 2004/0266688 A1	2004-12-30	Nayak	not required per 69 Fed. Reg. 56481
	4.	US 2005/0032699 A1	2005-02-10	Holash *et al.*	not required per 69 Fed. Reg. 56481
	5.	US 6,879,294 B2	2005-05-24	Davis-Smyth *et al.*	not required per 69 Fed. Reg. 56481
	6.	US 2005/0281822 A1	2005-12-22	Cedarbaum *et al.*	not required per 69 Fed. Reg. 56481
	7.	US 2006/0030000 A1	2006-02-09	Alitalo *et al.*	not required per 69 Fed. Reg. 56481
	8.	US 7,378,095 B2	2008-05-27	Cao *et al.*	not required per 69 Fed. Reg. 56481
	9.	US 7,482,002 B2	2009-01-27	Cedarbaum	not required per 69 Fed. Reg. 56481
	10.	US 2009/0264358 A1	2009-10-22	Yu	not required per 69 Fed. Reg. 56481
	11.	US 7,750,138 B2	2010-07-06	Fang *et al.*	not required per 69 Fed. Reg. 56481
	12.	US 7,951,585 B2	2011-05-31	Ke	not required per 69 Fed. Reg. 56481
	13.	US 8,216,575 B2	2012-07-10	Yu	not required per 69 Fed. Reg. 56481
	14.	US 2013/0295094 A1	2013-11-07	Yancopoulos	not required per 69 Fed. Reg. 56481
	15.	US 9,657,084 B2	2017-05-23	Ke *et al.*	not required per 69 Fed. Reg. 56481

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	16.	CN 1304427C	2007-03-14	China	Machine translation	Previously in US Application 17/072,417
	17.	CN 100502945C	2009-06-24	China	Corresponds to US 2009/0264358 A1	Previously in US Application 17/072,417
	18.	CN 100567325C	2009-12-09	China	Machine translation	Previously in US Application 17/072,417
	19.	WO 2012/097019	2012-07-19	WIPO	N/A	Previously in US Application 17/072,417
	20.	CN 102233132 B	2013-10-23	China	Machine translation	Previously in US Application 17/072,417

EXAMINER	DATE CONSIDERED

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	June 21, 2021	1647

FOREIGN PATENT DOCUMENTS						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	REFERENCE PROVIDED*
	21.	CN 102380096 B	2014-04-30	China	Machine translation	Previously in US Application 17/072,417
	22.	CN 103212075 B	2017-06-27	China	Machine translation	Previously in US Application 17/072,417
	23.	CN 107115294 A	2017-09-01	China	Machine translation	Previously in US Application 17/072,417

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	24.	Anonymous, Meeting Archive Titled "PA003 Eighteen-Month Results From an Extension Study of a Phase 2, Dose- and Interval-Ranging Study of VEGF Trap-Eye in Wet AMD," presented by David S Boyer, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	25.	Anonymous, Meeting Archive Titled "PA040 One-Year Results of the DA VINCI Study of VEGF Trap-Eye in Diabetic Macular Edema," presented by Diana V Do, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417
	26.	Anonymous, Meeting Archive Titled "PA080 One-Year Results of a Phase 2 Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration," presented by David S Boyer, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	27.	Anonymous, Meeting Archive Titled "PO259 OCT and Fluorescein Angiography Outcomes Through 1 Year for a Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Peter K Kaiser, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	28.	Anonymous, Meeting Archive Titled "PO260 VEGF Trap-Eye Vision-Specific Quality of Life Through 52 Weeks in Patients with Neovascular AMD in CLEAR-IT 2: A Phase 2 Clinical Trial," presented by Allen C Ho, MD at Moscone Center (October 2009)	Previously in US Application 17/072,417
	29.	Anonymous, Meeting Archive Titled "PO492 One-Year Results of the VIEW 1 and VIEW 2 Studies: VEGF Trap-Eye in Wet AMD," presented by David M Brown MD at Orange County Center (October 2011)	Previously in US Application 17/072,417
	30.	Anonymous, Meeting Archive Titled "PO549 The 6-Month (Primary Endpoint) Results of the Phase 3 GALILEO Study: VEGF Trap-Eye in Central Retinal Vein Occlusion," presented by Jean-Francois Korobelnik, MD at Orange County Convention Center (October 2011)	Previously in US Application 17/072,417

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

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	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	31.	Anonymous, Meeting Archive Titled "PO571 OCT and Fluorescein Angiographic Outcomes Through 1 Year for the Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular AMD," presented by Quan Dong Nguyen, MD at Georgia World Congress Center (November 2008)	Previously in US Application 17/072,417
	32.	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals," *Drugs and the Pharmaceutical Sciences*, 85:91-108 (1997)	Previously in US Application 17/072,417
	33.	Bressler, N. M. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group, "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2," *Arch. Ophthalmol.,* 119(2):198-207 (2001)	Previously in US Application 17/072,417
	34.	Brown *et al.*, "Ranibizumab for Diabetic Macular Edema (DME): 24-Month Efficacy and Safety Results of RISE - a Phase 3 Randomized Controlled Trial," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6647 *(April 2011)*	Previously in US Application 17/072,417
	35.	Brown *et al.*, "Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study," *Ophthalmology,* 118(8):1594-2049 (2011)	Previously in US Application 17/072,417
	36.	Cao *et al.*, "VEGF Trap Promotes Regression of Choroidal Neovascularization (CNV) and Inhibits Fibrosis and Inflammation in the Subretinal Matrigel CNV Model," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science,* 50:2979 (April 2009)	Previously in US Application 17/072,417
	37.	Center for Drug Evaluation and Research Application Number: 21-756 Medical Review(s) (December 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>	Previously in US Application 17/072,417
	38.	Center for Drug Evaluation and Research BLA Application Number: 125156 Medical Review, (June 2006) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_MedR.pdf>	Previously in US Application 17/072,417
	39.	Cheung *et al.*, "Combined anti-PIGF and anti-VEGF Therapy Ameliorates Pathological Neovascularization and Improves Retinal Revascularization in the Murine Model of Oxygen Induced Ischemic Retinopathy," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:6064 (April 2011)	Previously in US Application 17/072,417
	40.	Dixon *et al.*, "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," *Expert Opin. Investig. Drugs*, 18(10):1573-1580 (2009)	Previously in US Application 17/072,417

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	REGN-008CIPCON10	17/352,892
	APPLICANT	
	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

NON-PATENT LITERATURE DOCUMENTS			
		DOCUMENT (Including Author, Title, Date, Pertinent Pages, etc.)	REFERENCE PROVIDED*
	41.	The Eyetech Study Group, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration," *Ophthalmology*, 110(5):979-986 (May 2003)	Previously in US Application 17/072,417
	42.	Heier *et al.*, "Ranibizumab for Choroidal Neovascularization Secondary to Causes Other Than Age-Related Macular Degeneration: A Phase I Clinical Trial," *Ophthalmology*, 118(1):111-118 (January 2011)	Previously in US Application 17/072,417
	43.	Heier, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies," *Ophthalmology*, 123(11):2376-2385 (2016)	Previously in US Application 17/072,417
	44.	Herceptin label, September 1998	Previously in US Application 17/072,417
	45.	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)," v1 (March 17, 2008)	Previously in US Application 17/072,417
	46.	Ip *et al.*, "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5," *Arch. Ophthalmol.,* 127(9):1101-1114 (2009)	Previously in US Application 17/072,417
	47.	Kaiser, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema," *Br. J. Ophthalmol.*, 93(2):135-36 (February 2009)	Previously in US Application 17/072,417
	48.	Korobelnik *et al.*, "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion," *Ophthalmology,* 121(1):202-208 (2014)	Previously in US Application 17/072,417
	49.	Krzystolik *et al.*, "Prevention of Experimental Choroidal Neovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment," *Arch. Ophthalmol.*, 120(3):338-346 (Mar. 2002)	Previously in US Application 17/072,417
	50.	Lalwani, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT," *Retina Today* (May 2007)	Previously in US Application 17/072,417
	51.	Lobov *et al.*, "VEGF Trap Treatment Regresses Pathological Neovessels, Improves Revascularization and Reduces Retinal Ischemia in the Murine Oxygen-Induced Retinopathy (OIR) Model," ARVO Annual Meeting Abstract, *Investigative Ophthalmology & Visual Science*, 52:3128 (April 2011)	Previously in US Application 17/072,417
	52.	Lucentis Approval (June 30, 2006)	Previously in US Application 17/072,417
	53.	Lucentis Label Title, 7 pages, 06/2010 [Cited in Third Party Observations filed in parent application USSN 16/055,847 for which a copy is unavailable on PAIR]	Previously in US Application 17/072,417
	54.	Macular Photocoagulation Study Group, "Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial," *Arch. Ophthalmol.,* 109(9):1220-1231 (1991)	Previously in US Application 17/072,417

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NON-PATENT LITERATURE DOCUMENTS			
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	55.	Mitchell *et al.*, "Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials," *Brit. J. Ophthalmology,* 94:2-13 (2010) (first online publication on May 20, 2009)	Previously in US Application 17/072,417
	56.	Mitra *et al.*, "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions," *Expert Review in Ophthalmol.*, Taylor & Francis, GB 6(6):623-629 (January 2011)	Previously in US Application 17/072,417
	57.	Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration," *Biodrugs*, 24(3):183-194 (2010)	Previously in US Application 17/072,417
	58.	Nguyen *et al.*, "A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration," *Ophthalmology*, 113(9):1522e1-1522e14 (Sept 2006) (epub July 28, 2006)	Previously in US Application 17/072,417
	59.	Regeneron Pharmaceuticals Inc., "Regeneron Receives $20 Million Milestone Payment for Initiation of Phase 3 Study of VEGF Trap-Eye in Wet AMD," Media Release: 13 Aug 2007. Available from URL: http://www.regeneron.com	Previously in US Application 17/072,417
	60.	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema," poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	Previously in US Application 17/072,417
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	REGENERON PHARMACEUTICALS, INC.	
	FILING DATE	GROUP
	June 21, 2021	1647

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	74.	IPR2021-00881 dated November 10, 2021, for US 9,254,338 B2	Previously in US Application 17/072,417

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Inventor Information for 17/352892

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Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
17352892	21-Jun-2021	George YANCOPOULOS	REGN-008CIPCON10	5070

TITLE OF INVENTION :

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	134100	

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1200	$0	$1200	22-Mar-2022	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 500815 . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. THOMAS TRIOLO
2. Karl Bozicevic
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
REGENERON PHARMACEUTICALS, INC.	Tarrytown	NEW YORK	UNITED STATES	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Karl Bozicevic/	**Date**	01-12-2022
Name	Karl Bozicevic	**Registration Number**	28807

Electronic Patent Application Fee Transmittal

Application Number:	17352892
Filing Date:	21-Jun-2021
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-008CIPCON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt

EFS ID:	44730999
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	12-JAN-2022
Filing Date:	21-JUN-2021
Time Stamp:	17:33:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E20221BH33382937
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	62899 d27bfac8d8dbd7185fd7397a16ae1490e28f8a61	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	40522 9901a7bdf50a95413a3ca3e8eb929b6722b96c21	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	103421		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/352,892	02/22/2022	11253572	REGN-008CIPCON10	5070

96387 7590 02/02/2022

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

George YANCOPOULOS, Yorktown Heights, NY;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

To: docket@bozpat.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 96387

Feb 03, 2022 05:02:06 AM

Dear PAIR Customer:

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 96387 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17352892	ISSUE.NTF	02/02/2022	REGN-008CIPCON10

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Electronically Filed		
PETITION FOR CERTIFICATE OF CORRECTION Address to: Mail Stop Certificate of Correction Branch Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-008CIPCON10
	First Named Inventor	George D. Yancopoulos
	Patent Number	11,253,572
	Issue Date	February 22, 2022
	Application Number	17/352,892
	Filing Date	June 21, 2021
	Title: "*Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*"	

Sir:

Transmitted herewith for filing is a Certificate of Correction for the above-identified patent. This request is being submitted to correct typographical errors made during the printing of the patent in a manner that does not correspond to the language (specific symbol) shown in the originally filed specification.

It is believed that no fee is due since the error was made by the Patent and Trademark Office. If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815, order number REGN-008CIPCON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 4 March 2022

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,253,572

APPLICATION NO. : 17/352,892

ISSUE DATE : February 22, 2022

INVENTOR(S) : George D. Yancopoulos

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 15, lines 36-37, please correct the specification from “gained ETDRS” to read --gained ≥15 ETDRS--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Pkwy, Suite 200
Redwood City, California 94065

Electronic Acknowledgement Receipt

EFS ID:	45146528
Application Number:	17352892
International Application Number:	
Confirmation Number:	5070
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George YANCOPOULOS
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON10
Receipt Date:	04-MAR-2022
Filing Date:	21-JUN-2021
Time Stamp:	12:40:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	REGN-008CIPCON10_2022-03-04_Petition_COC.pdf	21458 ac6fb40bebcff9568a3d04842fc5545d9406c551	no	1

Warnings:

Information:					
2	Request for Certificate of Correction	REGN-008CIPCON10_2022-03-04_COC.pdf	27746 5aaa733f833f68c1ee30d87d5aaa7ac2690c6a70	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	49204	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,253,572 B2
APPLICATION NO. : 17/352892
DATED : February 22, 2022
INVENTOR(S) : Yancopoulos

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

At Column 15, Lines 36-37, please correct "gained ETDRS" to read --gained ≥15 ETDRS--.

Signed and Sealed this
Twenty-ninth Day of March, 2022

Drew Hirshfeld
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:22-cv-61	8/2/2022	Northern District of West Virginia

PLAINTIFF	DEFENDANT
REGENERON PHARMACEUTICALS, INC.	MYLAN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	See attached		
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
CHERYL DEAN RILEY	/s/ D. Kinsey	8/3/2022

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
7,070,959	July 4, 2006	Regeneron Pharmaceuticals, Inc.
9,222,106	December 29, 2015	Regeneron Pharmaceuticals, Inc.
9,254,338	February 9, 2016	Regeneron Pharmaceuticals, Inc.
9,669,069	June 6, 2017	Regeneron Pharmaceuticals, Inc.
9,816,110	November 14, 2017	Regeneron Pharmaceuticals, Inc.
10,130,681	November 20, 2018	Regeneron Pharmaceuticals, Inc.
10,406,226	September 10, 2019	Regeneron Pharmaceuticals, Inc.
10,415,055	September 17, 2019	Regeneron Pharmaceuticals, Inc.
10,464,992	November 5, 2019	Regeneron Pharmaceuticals, Inc.
10,669,594	June 2, 2020	Regeneron Pharmaceuticals, Inc.
10,857,205	December 8, 2020	Regeneron Pharmaceuticals, Inc.
10,888,601	January 12, 2021	Regeneron Pharmaceuticals, Inc.
10,927,342	February 23, 2021	Regeneron Pharmaceuticals, Inc.
10,973,879	April 13, 2021	Regeneron Pharmaceuticals, Inc.
11,053,280	July 6, 2021	Regeneron Pharmaceuticals, Inc.
11,066,458	July 20, 2021	Regeneron Pharmaceuticals, Inc.
11,084,865	August 10, 2021	Regeneron Pharmaceuticals, Inc.
11,104,715	August 31, 2021	Regeneron Pharmaceuticals, Inc.
11,174,283	November 16, 2021	Regeneron Pharmaceuticals, Inc.
11,186,625	November 30, 2021	Regeneron Pharmaceuticals, Inc.
11,253,572	February 22, 2022	Regeneron Pharmaceuticals, Inc.
11,299,532	April 12, 2022	Regeneron Pharmaceuticals, Inc.
11,306,135	April 19, 2022	Regeneron Pharmaceuticals, Inc.
11,332,771	May 17, 2022	Regeneron Pharmaceuticals, Inc.

Trials@uspto.gov
571-272-7822

Paper No. 3

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2022-01524
Patent 11,253,572

Mailed: September 28, 2022

Before Cathy Underwood, *Trial Paralegal*

NOTICE OF FILING DATE ACCORDED TO PETITION
AND
TIME FOR FILING PATENT OWNER PRELIMINARY RESPONSE

The petition for *inter partes* review, filed in the above proceeding has been accorded the filing date of September 9, 2022.

Patent Owner may file a preliminary response to the petition no later than three months from the date of this notice. The preliminary response is limited to setting forth the reasons why the requested review should not be instituted. Patent Owner may also file an election to waive the preliminary

response to expedite the proceeding. For more information, please consult the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 (Aug. 14, 2012), which is available on the Board Web site at http://www.uspto.gov/PTAB.

Patent Owner is advised of the requirement to submit mandatory notice information under 37 C.F.R. § 42.8(a)(2) within 21 days of service of the petition.

The parties are encouraged to use the heading on the first page of this Notice for all future filings in the proceeding.

The parties are advised that under 37 C.F.R. § 42.10(c), recognition of counsel pro hac vice requires a showing of good cause. The parties are authorized to file motions for pro hac vice admission under 37 C.F.R. § 42.10(c). Such motions shall be filed in accordance with the "Order -- Authorizing Motion for Pro Hac Vice Admission" in Case IPR2013-00639, Paper 7, a copy of which is available on the Board Web site under "Representative Orders, Decisions, and Notices." **The parties are reminded that, in order for any motion for *pro hac vice* admission to be considered by the Board, the requisite fees must first be paid.** The current fee schedule is available at https://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule.

The parties are reminded that unless otherwise permitted by 37 C.F.R. § 42.6(b)(2), all filings in this proceeding must be made electronically in Patent Trial and Appeal Board End to End (PTAB E2E), accessible from the Board Web site at http://www.uspto.gov/PTAB. To file documents, users must register with PTAB E2E. Information regarding how to register with and use PTAB E2E is available at the Board Web site.

If there are any questions pertaining to this notice, please contact Cathy Underwood at 571-272-8358 or the Patent Trial and Appeal Board at 571-272-7822.

PETITIONER:

Teresa Stanek Rea
Deborah H. Yellin
Shannon M. Lentz
CROWELL & MORING LLP
TRea@Crowell.com
DYellin@Crowell.com
SLentz@Crowell.com

PATENT OWNER:

Regeneron – Bozicevic Field & Francis LLP
201 Redwood Shores Parkway
Suite 200
Redwood City, CA 94065

NOTICE CONCERNING ALTERNATIVE DISPUTE RESOLUTION (ADR)

The Patent Trial and Appeal Board (PTAB) strongly encourages parties who are considering settlement to consider alternative dispute resolution as a means of settling the issues that may be raised in an AIA trial proceeding. Many AIA trials are settled prior to a Final Written Decision. Those considering settlement may wish to consider alternative dispute resolution techniques early in a proceeding to produce a quicker, mutually agreeable resolution of a dispute or to at least narrow the scope of matters in dispute. Alternative dispute resolution has the potential to save parties time and money.

Many non-profit organizations, both inside and outside the intellectual property field, offer alternative dispute resolution services. Listed below are the names and addresses of several such organizations. The listings are provided for the convenience of parties involved in cases before the PTAB; the PTAB does not sponsor or endorse any particular organization's alternative dispute resolution services. In addition, consideration may be given to utilizing independent alternative dispute resolution firms. Such firms may be located through a standard keyword Internet search.

CPR INSTITUTE FOR DISPUTE RESOLUTION	AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION (AIPLA)	AMERICAN ARBITRATION ASSOCIATION (AAA)	WORLD INTELLECTUAL PROPERTY ORGANIZATION (WIPO)	AMERICAN BAR ASSOCIATION (ABA)
Telephone: (212) 949-6490	Telephone: (703) 415-0780	Telephone: (212) 484-3266	Telephone: 41 22 338 9111	Telephone : (202) 662-1000
Fax: (212) 949-8859	Fax: (703) 415-0786	Fax: (212) 307-4387	Fax: 41 22 733 5428	N/A
575 Lexington Ave	241 18th Street, South, Suite 700	140 West 51st Street	34, chemin des Colombettes	1050 Connecticut Ave, NW
New York, NY 10022	Arlington, VA 22202	New York, NY 10020	CH-1211 Geneva 20, Switzerland	Washington D.C. 20036
www.cpradr.org	www.aipla.org	www.adr.org	www.wipo.int	www.americanbar.org

If parties to an AIA trial proceeding consider using alternative dispute resolution, the PTAB would like to know whether the parties ultimately decided to engage in alternative dispute resolution and the reasons why or why not. If the parties actually engage in alternative dispute resolution, the PTAB would be interested to learn what mechanism (e.g., arbitration,

mediation, etc.) was used and the general result. Such a statement from the parties is not required but would be helpful to the PTAB in assessing the value of alternative dispute resolution to parties involved in AIA trial proceedings. To report an experience with ADR, please forward a summary of the particulars to the following email address: PTAB_ADR_Comments@uspto.gov