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(54) USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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None

See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

6,171,586	B1	1/2001	Lam et al.
6,833,349	B2	12/2004	Xia et al.
6,879,294	B2	5/2005	Davis-Smyth et al.
6,897,294	B2	5/2005	Davis-Smyth et al.
7,070,959	B1	7/2006	Papadopoulos
7,303,746	B2	12/2007	Wiegand
7,303,747	B2	12/2007	Wiegand et al.
7,303,748	B2	12/2007	Wiegand
7,306,799	B2	12/2007	Wiegand
7,374,757	B2	5/2008	Papadopoulos et al
7,374,758	B2	5/2008	Papadopoulos et al
7,378,095	B2	5/2008	Cao et al.
7,396,664	B2	7/2008	Daly et al.
7,482,002	B2	1/2009	Cedarbaum
7,521,049	B2	4/2009	Wiegand et al.
7,531,173	B2	5/2009	Wiegand et al.
7,750,138	B2	7/2010	Fang et al.
7,951,585	B2	5/2011	Ke
8,092,803	B2	1/2012	Furfine et al.
		(Con	tinued)

FOREIGN PATENT DOCUMENTS

CN 1304427 C 3/2007 CN 100502945 C 6/2009 (Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 16/055,847—Third Party Submissions dated May 1, 2019.

(Continued)

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(57) ABSTRACT

The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks. The methods of the present invention are useful for the treatment of angiogenic eye disorders such as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

30 Claims, 1 Drawing Sheet



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U.S. PATENT DOCUMENTS

8,216,575	B2	7/2012	Yu
9,254,338	B2	2/2016	Yancopoulos
9,657,084	B2	5/2017	Ke et al.
9,669,069	B2	6/2017	Yancopoulos
10,130,681	B2	11/2018	Yancopoulos
10,406,226	B2	9/2019	Dix et al.
10,464,992	B2	11/2019	Furfine et al.
10,828,345	B2	11/2020	Yancopoulos
2003/0113316	A1	6/2003	Kaisheva et al.
2003/0138417	A1	7/2003	Kaisheva et al.
2003/0171320	A1	9/2003	Guyer
2004/0197324	A1	10/2004	Liu et al.
2004/0213787	A1	10/2004	Sleeman et al.
2004/0266688	A1	12/2004	Nayak
2005/0032699	A1	2/2005	Holash et al.
2005/0163798	A1	7/2005	Papadopoulos et al.
2005/0260203	A1	11/2005	Wiegand et al.
2005/0281822	A1	12/2005	Cedarbaum et al.
2006/0030000	A1	2/2006	Alitalo et al.
2006/0058234	A1	3/2006	Daly et al.
2006/0172944	A1	8/2006	Wiegand et al.
2006/0217311	A1	9/2006	Dix et al.
2007/0190058	A1	8/2007	Shams
2008/0220004	A1	9/2008	Wiegand et al.
2009/0264358	A1	10/2009	Yu
2013/0295094	A1	11/2013	Yancopoulos
2016/0130337	A1	5/2016	Gekkieva et al.
2019/0290725	A1	9/2019	Vitti et al.
2019/0388539	A1	12/2019	Dix et al.
2020/0017572	A1	1/2020	Furfine et al.

FOREIGN PATENT DOCUMENTS

CN	100567325 C	12/2009
$^{\rm CN}$	102233132 B	10/2013
CN	102380096 B	4/2014
CN	103212075 B	6/2017
CN	107115294 A	9/2017
EP	2663325	11/2013
JP	2010-509369	3/2010
WO	97/04801	2/1997
WO	WO 97/04801	2/1997
WO	WO 2000/75319	12/2000
WO	WO 2004/106378 A2	12/2004
WO	WO 2005/000895 A2	1/2005
WO	WO 2006/047325	3/2006
WO	WO 2007/022101 A2	2/2007
WO	WO 2008/063932	5/2008
WO	WO 2012/097019	7/2012

OTHER PUBLICATIONS

U.S. Appl. No. 16/159,282—Third Party Submissions dated May 31, 2019.

Adsis R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap—Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye." Drugs R D, 9(4):261-269 (2008).

Anonymous "Lucentis (rangibizymab injection) Intravitreal Injection" pp. 103 (Jun. 2006).

Anonymous "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published Aug. 5, 2019).

Barbazetto, "Dosing Regimen And The Frequency Of Macular Hemorrhages In Neovascular Age-Related Macular Degeneration Treated With Ranibizumab." Retina, 30(9):1376-85 (2010).

Bayer Investor News, "Bayer and Regeneron Start additional Phase 3 Study for VEGF Trap-Eye in Wet Age-related Macular Degeneration." (May 8, 2008).

Bayer Investor News, "VEGF Trap-Eye: New Data Confirm Successes in the Treatment of Age-related Macular Degeneration" (Sep. 28, 2008)

Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" ARVO Annual Meeting Abstract (May 2007).

Boyer, "A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration." Ophthalmology, 116(9):1731-39 (Sep. 2009).

Brown, "Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration." N Engl J Med, 355(14):1432-44 (Oct. 5, 2006).

Brown, "Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration." Ophthalmology, 118(6): 1089-97 (Jun. 2011).

Brown, "Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two phase III Trials." Ophthalmology, 120(10):2013-22 (Oct. 2013).

Browning et al. "Affibercept for age-related macular degeneration: a game-changer or quiet addition?" American Journal of Ophthalmology, 154(2):222-226 (Aug. 2012).

Campochiaro et al. "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions Implication of VEGF as a Critical Stimulator" Molecular Therapy, 16(4):791-799 (2008).

Campochiaro, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion: six-month primary end point results of a phase III study." Ophthalmology, 117(6):1102-1112 (Jun. 2010).

Campochiaro, "Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a phase III Study." Ophthalmology, 188(10):2041-49 (Oct. 2011).

Cao, "A Subretinal Matrigel Rat Choroidal Neovascularization (CNV) Model and Inhibition of CNV and Associated Inflammation and Fibrosis by VEGF Trap" Investigative Ophthalmology & Visual Science, 51 (11):6009-6017 (Nov. 2010).

Center for Drug Evaluation and Research BLA Application No. 125156 Medical Review, (Jun. 2006) < URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>.

Charles, Steve (Guest Lecturer) "VEGF Trap Has Positive DME Data" Tenth Annual Retina Fellows Forum Jan. 29 and 30, Chicago, (Article Date Mar. 1, 2010).

Chatziralli et al. "Intravitreal aflibercept for neovascular age-related macular degeneration in patients aged 90 years or older: 2-year visual acuity outcomes" Eye (2018) 32:1523-1529.

Chung et al. "Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer" Am J Heath-Syst Pharm (Nov. 1, 2013) 70:1887-1896.

Cooper et al., "Increased Renal Expression of Vascular Endothelial Growth Factor (VEGF) and Its Receptor VEGFR-2 in Experimental Diabetes" Diabetes (1999) 48:2229-2239.

Croll et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402.

Csaky, "Safety Implications of Vascular Endothelial Growth Factor Blockade for Subjects Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapies." Am. J. Ophthalmology, 148(5):647-56, (Nov. 2000)

DeVriese et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000.

Do et al., "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema" Br J Ophthalmol. 93(2):144-1449 (Feb. 2009).

Do et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Ophthalmology, 118(9): 1819-1826 (Sep. 2011).

Do, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." Ophthalmology, 119(8):1658-65 (2012).

Do et al. "Results of a Phase 1 Study of Intravitreal VEGF Trap in



OTHER PUBLICATIONS

Do et al. "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" ARVO Annual Meeting Abstract (Apr. 2000)

Eichten, "Rapid decrease in tumor perfusion following VEGF blockade predicts long-term tumor growth inhibition in preclinical tumor models" Angiogenesis, 16:429-441 (2013).

Engelbert, "Treat And Extend' Dosing Of Intravitreal Antivascular Endothelial Growth Factor Therapy For Type 3 Neovascularization/ Retinal Angiomatous Proliferation." Retina, 29(10):1424-31 (2009). Engelbert, "Long-Term Follow-Up For Type 1 (Subretinal Pigment Epithelium) Neovascularization Using A Modified 'Treat And Extend' Dosing Regiment Of Intravitreal Antivascular Endothelial Growth Factor Therapy." Retina, 30(9):1368-75 (2010).

Engelbert, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." Ophthalmology Management, Issue 42, (Jun. 2010) available at http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42.

Eremina et al., "Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases" Journal of Clinical Investigation (Mar. 2003) 111(5):707-716.

Eriksson et al., "Structure, Expression and Receptor-Binding Properties of Novel Vascular Endothelial Growth Factors" Vascular Growth Factors and Angiogenesis, Springer (1999) pp. 41-57.

The Eyetech Study Group, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthalmology, 110(5):979-986 (May 2003).

Eylea®, Highlights of Prescribing Information, Revised Aug. 2018. Ferrara, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30. Ferrara et al., "Clinical applications of angiogenic growth factors and their inhibitors" Nature Medicine (Dec. 1999) 5(12):1359-1364. Flyvbjerg et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (Oct. 2002) 51:3090-3094.

Fung, "An Optical Coherence Tomography-Guided, Variable Dosing Regiment with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration." Am J Ophthalmology, 143(4):566-83 (Apr. 2007).

Gale, "Complementary and Coordinated Roles of the VEGFs and Angiopoietins during Normal and Pathologic Vascular Formation." Cold Spring Harbor Symposia on Quantitative Biology, vol. LXVIL, pp. 267-273 (2002).

Garcia-Quintanilla, "Pharmacokinetics of Intravitreal Anti-VEGF Drugs in Age-Related Macular Degeneration." Pharmaceutics, 11:365 (2019).

Gomez-Manzano, "VEGF Trap induces antiglioma effect at different stages of disease." Neuro-Oncology, 10:940-945 (Dec. 2008). Gragoudas, "Pegaptanib for Neovascular Age-Related Macular Degeneration." N Engl J Med, 351(27):2805-16, (Dec. 30, 2004).

Gutierrez et al., "Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion" Clin. Ophthalmol., 2(4):787,791 (2008).

Haller et al., "VEGF Trap-Eye In CRVO: Primary Endpoint Results of the Phase 3 COPERNICUS Study" ARVO Annual Meeting Abstract (Apr. 2011).

Heier et al., "CLEAR-IT 2: Phase 2, Randomized Controlled Dose and Interval-Ranging Study of Intravitreal VEFG Trap Eye in Patients with Neovascular Age-Related Macular Degeneration: Predictive Factors for Visual Acuity" ARVO Annual Meeting Abstract (Apr. 2009).

Heier, J., "Intravitreal VEGF Trap for AMD: An Update, The CLEAR-IT 2 Extension Study" Presented at the annual meeting of

Heier et al., "rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002).

Heier et al., "RhuFab V2 in Wet AMD—6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44(E-Abstract):972 (2003).

Heier et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012).

Heier, "Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." Ophthalmology, 123(11):2376-2385 (Nov. 2016).

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 2011;118:1098-1106 (Jun. 2011).

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: Erratum" Ophthalmology 2011;118:1700 (Sep. 2011).

Ho, "VEGF Trap-Eye in Wet AMD—CLEAR-IT 2: One-Year OCT and FA Outcomes" CLEAR-IT 2 Study Group, pp. 1-24 (Sep. 28, 2008).

Ho et al., Slides entitled CLEAR IT 2 One-Year Key Results, Retina Society (2008).

Holash et al., "Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VEGF" Science (Jun. 18, 1999) 284(5422):1994-1998.

Holash, "VEGF-Trap: A VEGF blocker with potent antitumor effects" PNAS 99(17)11393-11398 (Aug. 20, 2002).

Holash, "Inhibitors of growth factor receptors, signaling pathways and angiogenesis as therapeutic molecular agents." Cancer Metastasis 25:243-252 (2006).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 70 pages, Latest version submitted Jun. 8, 2011 on ClinicalTrials.gov (NCT00320775_2006-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320775 "Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration" 10 pages, Latest version submitted Mar. 16, 2015 on ClinicalTrials.gov (NCT00320775_2015).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320788 "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)" 71 pages, Latest version submitted Dec. 1, 2011 on ClinicalTrials.gov (NCT00320788_2006-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320788 "Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)" 31 pages, Latest version submitted Jan. 27, 2012 on ClinicalTrials.gov (NCT00320788_2012).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00320814 "Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema" 30 pages, Latest version submitted Jun. 8, 2011 on ClinicalTrials.gov (NCT00320814_2006-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00509795 "Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)" 318 pages, Latest version submitted Dec. 1, 2011 on ClinicalTrials.gov (NCT00509795_2007-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00509795 "Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)" 200 pages, Latest version submitted Dec. 20, 2012 on ClinicalTrials.gov (NCT00509795 2012).



OTHER PUBLICATIONS

Safety and Tolerability Study of VEGF Trap-Eye in AMD" 64 pages, Latest version submitted Nov. 1, 2011 on ClinicalTrials.gov (NCT00527423 2007-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00527423 "Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD" 42 pages, Latest version submitted Jun. 10, 2013 on ClinicalTrials.gov (NCT00527423 2012-2013).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 667 pages, Latest version submitted Dec. 16, 2011 on ClinicalTrials.gov (NCT00637377_2008-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" 289 pages, Latest version submitted Nov. 28, 2014 on ClinicalTrials.gov (NCT00637377_2012-2014).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 135 pages, Latest version submitted May 2, 2011 on ClinicalTrials.gov (NCT00789477_2008-2011). Information from ClinicalTrials.gov archive History of Changes for Study: NCT00789477 "DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)" 53 pages, Latest version submitted Aug. 28, 2014 on ClinicalTrials.gov (NCT00789477_2013-2014). Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 98 pages, Latest version submitted May 9, 2011 on ClinicalTrials.gov (NCT00943072_2009-2011).

Information from ClinicalTrials.gov archive History of Changes for Study: NCT00943072 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)" 64 pages, Latest version submitted Apr. 16, 2013 on ClinicalTrials.gov (NCT00943072_2012-2013).

Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" ClinicalTrials.gov. Web. (Nov. 30, 2010). Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available (updated on Mar. 17, 2008).

Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (Dec. 1, 2009).

Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (Nov. 18, 2010).

Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (Jan. 7, 2011).

Information from ClinicalTrials.gov archive on the view of NCT01012973 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 7 pages, first posted Nov. 13, 2009; results first posted Nov. 22, 2012; last update posted Nov. 3, 2014; printed Dec. 4, 2019 (https://clinicaltrials.gov/ct2/show/study/NCT01012973) (NOTE: May correspond to "Vascular Endothelial Growth Factor Trap‐ Eye Investigation of Efficacy and

cation U.S. Appl. No. 16/055,847]" which was cited in the Third Party Observations dated May 1, 2019).

Karia, Niral, "Retinal vein occlusion: pathophysiology and treatment options" Clinical Ophthalmology, 4:809-816 (2010).

Korobelnik et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" American Academy of Ophthalmology (2014) 121 (1):202-208.

Korobelnik, "Intravitreal Aflibercept for Diabetic Macular Edema." Ophthalmology, 121(11):2247-54 (Nov. 2014).

Kuo, "Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer" PNAS 98(8):4605-4610 (Apr. 10, 2001).

Krzystolik et al., "Prevention of Experimental Choroidal NEovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" Arch Ophthamol., 120:338-346 (Mar. 2002).

Lalwani, A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-related Macular Degeneration: Year 2 of the PrONTO Study. Am J Ophthalmology, 148(1):43-58 (Jul. 2009). Levine, "Macular Hemorrhage In Neovascular Age-Related Macular Degeneration After Stabilization With Antiangiogenic Therapy." Retina, 29(8):1074-79 (2009).

Lucentis Label Title, 7 pages, Jun. 30, 2010 [Cited in Third Party Observations filed in parent application U.S. Appl. No. 16/055,847]. Major et al., "DA VINCI: DME and VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 Study in Patients with Diabetic Macular Edema (DME)" ARVO Annual Meeting Abstract (Apr. 2010).

Margolis, "Hemorrhagic Recurrence Of Neovascular Age-Related Macular Degeneration Not Predicted By Spectral Domain Optical Coherence Tomography." Retinal Cases & Brief Reports, 4:1-4 (2010).

Massin, "Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study*)." Diabetes Care, 33(11):2399-405 (Nov. 2010).

Mitchell, "The RESTORE Study, Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema." Ophthalmology, 188(4):615-25 (Apr. 2011).

Mitchell, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85.

N/A "Materials from Jun. 2011 FDA Committee Mtg" (Jun. 17, 2011).

N/A "Materials from Dec. 2011 FDA Committee Mtg" (Dec. 1, 2011).

Nguyen et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" Opthamology, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (Nov. 1, 2009).

Nguyen et al., "Randomized, Double-masked, Active-controlled Phase 3 Trial of the Efficacy and Safety of Intravitreal VEGF Trap-Eye in Wet AMD: One-year Results of the VIEW 1 Study" ARVO Annual Meeting Abstract (Apr. 2011).

Nguyen, "Ranibizumab for Diabetic Macular Edema, Results from 2 Phase III Randomized Trials: RISE and RIDE." Ophthalmology, 119(4):789-801 (Apr. 2012).

Nguyen et al., "Results of a Phase I, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreous VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (May 2006).

Nichols, Earl R., "AAO: Ranibizumab (rhuRab) May Improve Vision in Age-Related Macular Degeneration" Doctor's Guide Global Edition, www.pslgroup.com/dg/23f2aa.htm, pp. 1-2 (Nov. 24, 2003).

Noguera-Troise et al., "Blockade of D114 inhibits tumour growth by promoting non-productive angiogenesis" Nature (Dec. 2006) 444:1032-1037.

Ohr, "Aflibercept in wet age-related macular degeneration: a perspective review" Ther. Adv. Chronic Dis., 3(4):153-161 (2012). Olivera et al., "VEGF Trap R1R2 suppresses experimental corneal



OTHER PUBLICATIONS

Pai et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Ophthalmology 24(4):143-149 (Jun. 30, 2010).

Papadppoulos, "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab" Angiogenesis, 15:171-185 (2012).

Regeneron SEC Form 10-K (Feb. 27, 2008).

Regeneron SEC Form 10-K (Feb. 26, 2009).

Regeneron SEC Form 10-K (Feb. 17, 2011).

Regeneron SEC Form 10-Q (May 8, 2006).

Regeneron SEC Form 10-Q (Aug. 8, 2006).

Regeneron SEC Form 10-Q (Nov. 6, 2006).

Regeneron SEC Form 10-Q (May 4, 2007).

Regeneron SEC Form 10-Q (Aug. 3, 2007).

Regeneron SEC Form 10-Q (Apr. 30, 2009).

Regeneron SEC Form 10-Q (Nov. 3, 2009).

Regeneron SEC Form 10-Q (Apr. 29, 2010).

Regeneron SEC Form 10-Q (Jul. 28, 2010).

Regeneron SEC Form 10-Q (Oct. 28, 2010).

Regeneron SEC Form 10-Q (May 3, 2011).

Regeneron SEC Form 10-Q (Jul. 28, 2011).

Regeneron SEC Form 10-Q (Oct. 27, 2011).

Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron

Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006).

Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006).

Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on Jun. 9, 2006" (Jun. 9, 2006).

Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007).

Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on Jun. 8, 2007" (Jun. 8, 2007).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Oct. 1, 2007" (Oct. 1, 2007).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Nov. 6, 2007" (Nov. 6, 2007).

Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Nov. 4, 2008" (Nov. 4, 2008).

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 Jan. 12-15, 2009." (Jan. 9, 2009).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Apr. 30, 2009" (May 1, 2009).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Nov. 3, 2009." (Nov. 4, 2009).

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 Dec. 20, 2010." (Dec. 20, 2010).

Regeneron SEC Form 8-K Exhibit: "Press Release dated Feb. 17, 2011" (Feb. 18, 2011).

Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion, dated Apr. 27, 2011" (Apr. 27, 2011). Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3,

2011." (May 3, 2011).

Regeneron SEC Form 8-K Exhibit: "Press Release, dated Jun. 17, 2011, Announcing that EYLEATM (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (Jun. 21, 2011).

Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF

Regeneron SEC Form 8-K Exhibit: "Press Release Announcing FDA Approval of EYLEATM (affibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, dated Nov. 18, 2011" (Nov. 21, 2011).

Regeneron Press Release "Positive Interim Phase 2 Data Reported For VEGF Trap-Eye In Age-Related Macular Degeneration" (Mar. 27, 2007).

Regeneron Press Release "VEGF TRAP-Eye Phase 2 Wet AMD Results Reported At Arvo Annual Meeting" (May 9, 2007).

Regeneron Press Release "Regeneron Reports Second Quarter Financial And Operating Results" (Aug. 1, 2007).

Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Healthcare Initiate Phase 3 Global Development Program for VEGF Trap-Eye In Wet Age-Related Macular Degeneration (AMD)" (Aug. 2 2007)

Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on Nov. 7, 2007 for the period ending Sep. 30, 2007.

Regeneron Press Release "Regeneron Announces Positive Primary Endpoint Results From A Phase 2 Study Of VEGF Trap-Eye In Age-Related Macular Degeneration" (Oct. 1, 2007).

Regeneron Press Release "Regeneron Reports Fourth Quarter And Full Year 2007 Financial And Operating Results" (Feb. 27, 2008). Regeneron Pharmaceuticals, Inc., "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" (Apr. 28, 2008).

Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.

Regeneron 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.

Regeneron Pharmaceuticals, Inc., "Regeneron and Bayer Health-care Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Agerelated Macular Degeneration" (Aug. 19, 2008).

Regeneron Pharmaceuticals Inc., "VIEW 1 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (Feb. 12, 2011).

Regeneron Pharmaceuticals Inc., "VIEW 2 Vascular Endothelial Growth Factor (VEGF) Trap-Eye 1-Year Results: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" presented at Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting in Miami, Florida (Feb. 12, 2011).

Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (Sep. 30, 2007).

Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (Sep. 28, 2008) (XP-002770952).

Regeneron 2008 Annual Report.

Regeneron Pharmaceuticals, Inc. "Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results" (Feb. 26, 2009).

Regeneron Pharmaceuticals, Inc. "Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion" (Apr. 30, 2009).

Regeneron Press Release "First Patient Enrolled In Regeneron And Bayer Healthcare VEGF Trap-Eye Phase 3 Program In Central Retinal Vein Occlusion" (Jul. 23, 2009).

Regeneron Press Release "Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)" Sep. 14, 2009. Regeneron 2009 Annual Report and 10-K.

Regeneron Press Release, "VEGF Trap-Eye Shows Positive Results



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