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

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(58) **Field of Classification Search**

(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
7,087,411	B2	8/2006	Daly et al.
7,300,563	B2	11/2007	Diaddario, Jr.
7,300,653	B2	11/2007	Wiegand et al.
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.
7,608,261	B2	10/2009	Furfine et al.
7,750,138	B2	7/2010	Fang et al.
7,951,585	B2	5/2011	Ke
7,972,598	B2	7/2011	Daly et al.
8,029,791	B2	10/2011	Papadopoulos et al.
8,092,803	B2	1/2012	Furfine et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN	1304427 C	3/2007
CN	100502945 C	6/2009

(Continued)

OTHER PUBLICATIONS

Eylea®, Highlights of Prescribing Information, Revised Nov. 2011.

(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.

41 Claims, 1 Drawing Sheet

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,216,575	B2	7/2012	Yu
8,343,737	B2	1/2013	Papadopoulos et al.
8,647,842	B2	2/2014	Papadopoulos et al.
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
10,857,205	B2	12/2020	Yancopoulos
10,888,601	B2	1/2021	Yancopoulos
11,066,458	B2	7/2021	Furfine et al.
11,084,865	B2	8/2021	Furfine et al.
11,253,572	B2	2/2022	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
2010/0160233	A1	6/2010	Bissery et al.
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
CN	102233132	B	10/2013
CN	102380096	B	4/2014
CN	103212075	B	6/2017
CN	107115294	A	9/2017
EP	2663325		11/2013
EP	3222285	A1	9/2017
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

IPR2021-00880, Paper 1, Petition for IPR (May 5, 2021).
IPR2021-00880, Exhibit 1002, Albini Declaration (May 4, 2021).
IPR2021-00880, Exhibit 1003, Gerritsen Declaration (Apr. 30, 2021).
IPR2021-00880, Paper 10, Preliminary Response of Patent Owner (Aug. 16, 2021).
IPR2021-00881, Paper 1, Petition for IPR (May 5, 2021).
IPR2021-00881, Exhibit 1002, Albini Declaration (May 4, 2021).
IPR2021-00881, Exhibit 1003, Gerritsen Declaration (Apr. 26, 2021).
IPR2021-00881, Exhibit 2001, Do Declaration (Aug. 13, 2021).
Mitchell et al., "Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies" Ophthalmol Retina 2(10):988-96 (2018).
PGR2021-00035, Paper 2, Petition for PGR (Jan. 7, 2021).
PGR2021-00035, Paper 6, Preliminary Response of Patent Owner (Apr. 15, 2021).
PGR2021-00035, Exhibit 1003 Wu Declaration (Jan. 7, 2021).
PGR2021-00035, Exhibit 2001 Do Declaration (Apr. 14, 2021).
PGR2021-00035, Exhibit 2002 D. Brown Declaration (Apr. 14, 2021).
Cao, J. R., R.; Wang, Q.; Yancopoulos, G.D.; Wiegand, S.J. (2002). Inhibition of Corneal Neovascularization and Inflammation by VEGF Trap. In "ARVO", Invest. Ophthalmol. Vis. Sci. vol. 43. E-Abstract 1863.
Wang, Q. R., R.; Cao, J.; Yancopoulos, G.D.; and Wiegand, S.J. (2002). Anti-Angiogenic Properties of a New VEGF Antagonist, VEGF Trap, in a Mouse Model of Retinal Neovascularization. In "ARVO", Invest. Ophthalmol. Vis. Sci., vol. 43. E-Abstract. 3714.
Saishin, Y., Saishin, Y., Takahashi, K., Lima e Silva, R., et al. (2003). VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol 195:241-48.
Cursiefen, C., Cao, J., Chen, L., Liu, Y., Maruyama, K., et al. (2004). Inhibition of hemangiogenesis and lymphangiogenesis after normal-risk corneal transplantation by neutralizing VEGF promotes graft survival. Invest Ophthalmol Vis Sci 45(8):2666-73.
Cursiefen, C., Chen, L., Borges, L. P., Jackson, D., Cao, J., et al. (2004). VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. J Clin Invest 113(7):1040-50.
Cao, J.; Song, H.; Renard, R.A.; Liu, Y.; Yancopolous, G.D.; Wiegand, S.J. (2005). Systemic Administration of VEGF Trap Suppresses Vascular Leak and Leukostasis in the Retinas of Diabetic Rats. In "ARVO", vol. 46. Invest. Ophthalmol. Vis. Sci. E-Abstract 446.
Nork, T. M., Dubielzig, R. R., Christian, B. J., Miller, P. E., Miller, J. M., et al. (2011). Prevention of experimental choroidal neovascularization and resolution of active lesions by VEGF trap in nonhuman primates. Arch Ophthalmol 129(8):1042-52.
U.S. Appl. No. 16/055,847—Third Party Submissions dated May 1, 2019.
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 Hemorrhagesi 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).
Benz et al. "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)" 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-

(56) **References Cited**

OTHER PUBLICATIONS

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. "Aflibercept 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 Application No. 21-756 Medical Review(s) (Dec. 17, 2004) <URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>.
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. 2009).
DeVriese et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000.
Dixon et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" Expert Opin. Investig. Drugs, 18(10):1573-1580 (2009).
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 Ds 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
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. 2009).
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 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

(56) **References Cited**

OTHER PUBLICATIONS

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).
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" 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
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 Safety in Central Retinal Vein Occlusion title, 8 pages, Nov. 12, 2009, US [Cited in Third Party Observations filed in parent U.S. Appl. No. 16/055,847]" which was cited in the Third Party Observations dated May 1, 2019).
Kaiser, "Vascular endothelial growth factor Trap-Eye for diabetic macular oedema." Br. J. Ophthalmol, 93(2):135-36 (Feb. 2009).
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.

(56) **References Cited**

OTHER PUBLICATIONS

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, "All About PrONTO: Study Yielded Good Results in AMD With Treatment Guided by OCT." Retina Today (May 2007).
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 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.
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 (Jan. 2011).
Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" Biodrugs; 24(3); 183-194 (2010).
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., "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 (Sep. 2006) (epub Jul. 28, 2006).
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
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 angiogenesis" European Journal of Ophthalmology, 20(1):48-54 (Jan. 1, 2010).
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 EYLEA™ (aflibercept ophthalmic solution)

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