



US010828345B2

(12) **United States Patent**  
**Yancopoulos**(10) **Patent No.:** **US 10,828,345 B2**(45) **Date of Patent:** **\*Nov. 10, 2020**(54) **USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS**(71) Applicant: **REGENERON PHARMACEUTICALS, INC.**,  
Tarrytown, NY (US)(72) Inventor: **George D. Yancopoulos**, Yorktown Heights, NY (US)(73) Assignee: **REGENERON PHARMACEUTICALS, INC.**,  
Tarrytown, NY (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/159,282**(22) Filed: **Oct. 12, 2018**(65) **Prior Publication Data**

US 2019/0046609 A1 Feb. 14, 2019

**Related U.S. Application Data**

(63) Continuation of application No. 15/471,506, filed on Mar. 28, 2017, now Pat. No. 10,130,681, which is a continuation of application No. 14/972,560, filed on Dec. 17, 2015, now Pat. No. 9,669,069, which is a continuation of application No. 13/940,370, filed on Jul. 12, 2013, now Pat. No. 9,254,338, which is a continuation-in-part of application No. PCT/US2012/020855, filed on Jan. 11, 2012.

(60) Provisional application No. 61/432,245, filed on Jan. 13, 2011, provisional application No. 61/434,836, filed on Jan. 21, 2011, provisional application No. 61/561,957, filed on Nov. 21, 2011.

(51) **Int. Cl.****A61K 38/17** (2006.01)**A61K 38/18** (2006.01)**C07K 14/71** (2006.01)**C07K 16/22** (2006.01)**A61K 9/00** (2006.01)**A61K 39/00** (2006.01)(52) **U.S. Cl.**CPC ..... **A61K 38/179** (2013.01); **A61K 9/0048** (2013.01); **C07K 14/71** (2013.01); **C07K 16/22** (2013.01); **A61K 2039/505** (2013.01); **C07K 2319/30** (2013.01); **C07K 2319/32** (2013.01)(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**7,070,959 B1 7/2006 Papadopoulos  
7,303,746 B2 12/2007 Wiegand7,303,748 B2 12/2007 Wiegand  
7,306,799 B2 12/2007 Wiegand  
7,396,664 B2 7/2008 Daly et al.  
8,092,803 B2 1/2012 Furfine et al.  
9,254,338 B2 2/2016 Yancopoulos  
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.  
2003/0171320 A1 9/2003 Guyer  
2005/0163798 A1 7/2005 Papadopoulos et al.  
2005/0260203 A1 11/2005 Wiegand et al.  
2006/0058234 A1 3/2006 Daly et al.  
2006/0172944 A1 8/2006 Wiegand et al.  
2007/0190058 A1 8/2007 Shams  
2008/0220004 A1 9/2008 Wiegand 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**JP 2010-509369 3/2010  
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**Anonymous "Lucentis (ranibizumab injection) Intravitreal Injection" pp. 103 (Jun. 2006).  
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.  
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>.

(Continued)

*Primary Examiner* — Christine J Saoud*Assistant Examiner* — Jon M Lockard(74) *Attorney, Agent, or Firm* — Thomas Triolo; Karl Bozicevic(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.

**11 Claims, 1 Drawing Sheet****Specification includes a Sequence Listing.**

(56)

## References Cited

## OTHER PUBLICATIONS

- 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.
- Dixon et al., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration" *Expert Opin. Investig. Drugs* (2009) 18 (10): 1-8.
- 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).
- 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).
- 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).
- 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 and 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).
- Krzysztofik et al., "Prevention of Experimental Choroidal Neovascularization With Intravitreal Anti-Vascular Endothelial Growth Factor Antibody Fragment" *Arch Ophthalmol.*, 120:338-346 (Mar. 2002).
- Mitra et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" *Expert Review in Ophthalmology*, Taylor & Francis, GB (Jan. 1, 2011) 6(6):623-629.
- Mousa and Mousa, "Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration" *Biodrugs* 2010; 24(3): 183-194.
- Nguyen et al., "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration" *Ophthalmology*, J.B. Lippincott Co., Philadelphia, PA, US, 116(11):2141-2148 (Nov. 1, 2009) 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* (Sep. 2006) 113(9):1522e1-1522e14 (epub Jul. 28, 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, 20013).
- Olivera et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" *European Journal of Ophthalmology* (Jan. 1, 2010) 20(1):48-54.
- Pai et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" *Saudi Journal of Ophthalmology* 24(4):143-149 (Jun. 30, 2010).
- Regeneron Pharmaceuticals, Inc. Form 10-Q, published on Nov. 7, 2007 for the period ending Sep. 30, 2007.
- Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.
- Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" Nov. 22, 2010.
- Regeneron Press Release "Regeneron and Bayer Report 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)" Dec. 20, 2010.
- 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).
- Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy" *Diabetes Care*, vol. 32, No. 8, Aug. 2009.
- Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", Sep. 28, 2008.
- Stewart, "The expanding role of vascular endothelial growth factor inhibitors in ophthalmology" *Mayo Clin Proc.* 87(1):77-88 (Jan. 2012).
- Thomas Reuters Integrity "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (Sep. 28, 2008).
- WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" vol. 20, No. 2, 2006, pp. 115-119.
- 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.
- 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*, 2013.
- Campochiaro, "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion." *Ophthalmology*, 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.
- 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.
- Do, "One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema." *Ophthalmology*, 2012.
- Engelbert, "The 'Treat and Extend' Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration." *Ophthalmology Management*, Jun. 2010, available at <http://www.visioncareprofessional.com/emails/amupdate/index.asp?issue=42>.
- Engelbert, "Long-Term Follow-Up for Type 1 (Subretinal Pigment Epithelium) Neovascularization Using a Modified 'Treat and Extend'

(56)

## References Cited

## OTHER PUBLICATIONS

- Dosing Regimen of Intravitreal Antivasular Endothelial Growth Factor Therapy." *Retina*, 30:9, 1368-75, 2010.
- Engelbert, "'Treat and Extend' Dosing of Intravitreal Antivasular Endothelial Growth Factor Therapy for Type 3 Neovascularization/Retinal Angiomatous Proliferation." *Retina*, 29:10, 1424-31, 2009.
- Eylea®, Highlights of Prescribing Information, Revised Aug. 2018.
- Fung, "An Optical Coherence Tomography-Guided, Variable Dosing Regimen 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. LXVII, pp. 267-73, 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." *Society for Neuro-Oncology*, Dec. 2008.
- Gragoudas, "Pegaptanib for Neovascular Age-Related Macular Degeneration." *N Engl J Med* 351:27, 2805-16, Dec. 30, 2004.
- Heier, "Intravitreal Aflibercept for Diabetic Macular Edema." *Ophthalmology*, 2016.
- Ho et al., Slides entitled CLEAR IT 2 One-Year Key Results, Retina Society 2008.
- Korobelnik, "Intravitreal Aflibercept for Diabetic Macular Edema." *Ophthalmology*, 121:11, 2247-54, Nov. 2014.
- 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.
- Margolis, "Hemorrhagic Recurrence of Neovascular Age-Related Macular Degeneration Not Predicted by Spectral Domain Optical Coherence Tomography." *Retinal Cases & Brief Reports*, 4:1, 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.
- Nguyen, "Ranibizumab for Diabetic Macular Edema, Results from 2 Phase III Randomized Trials: RISE and RIDE." *Ophthalmology*, 119:4, 789-801, Apr. 2012.
- 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 Press Release, "VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema." Feb. 18, 2010.
- Rosenfeld, "Ranibizumab for Neovascular Age-Related Macular Degeneration." *N Engl J Med*, 355:14, 1419-31, Oct. 5, 2006.
- Rosenfeld, "Lessons Learned From Avastin and OCT-The Great, the Good, the Bad, and the Ugly: The LXXV Edward Jackson Memorial Lecture." *Am. J. Ophthalmology*, 204:26-45, Aug. 2019.
- Schmidt-Erfurth, "Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration." *Ophthalmology*, 2010.
- Schmidt-Erfurth, "Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema." *Ophthalmology*, 121:5, 1045-53, May 2014.
- Spaide, "Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration." *Am J Ophthalmology*, Apr. 2007.
- Wolfson, "Regeneron Focuses on Age-Related Macular Degeneration." *Chemistry & Biology* 15:303-304, Apr. 2008.
- Yancopoulos, "Vascular-specific growth factors and blood vessel formation." *Nature* 407:242-48, Sep. 14, 2000.
- Yancopoulos, "Clinical Application of Therapies Targeting VEGF." *Cell* 143, Oct. 1, 2010.
- Yung, "moving Toward the Next Steps in Angiogenesis Therapy?" *Society for Neuro-Oncology*, 10:939, 2008.
- Browning et al. "Aflibercept for age-related macular degeneration: a game-changer or quiet addition?" *American Journal of Ophthalmology*, vol. 154(2):222-226 (Aug. 1, 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).
- 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).
- Eichten, "Rapid decrease in tumor perfusion following VEGF blockade predicts long-term tumor growth inhibition in preclinical tumor models" *Angiogenesis*, 16:429-441 (2013).
- 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).
- 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).
- Karia, Niral, "Retinal vein occlusion: pathophysiology and treatment options" *Clinical Ophthalmology*, 4:809-816 (2010).
- Kuo, "Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer" *PNAS* 98(8):4605-4610 (Apr. 10, 2001).
- Lucentis Label Title, 7 pages, Jun. 30, 2010 [Cited in Third Party Observations filed in parent U.S. Appl. No. 16/055,847].
- Ohr, "Aflibercept in wet age-related macular degeneration: a perspective review" *Ther. Adv. Chronic Dis.*, 3(4):153-161 (2012).
- Papadopoulos, "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab" *Angiogenesis*, 15:171-185 (2012).
- Regillo et al., "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: OIER Study Year 1" *American Journal of Ophthalmology*, 145(2):239-248 (2008).
- Schnichels, "Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells." *Br. J. Ophthalmol.* (May 17, 2013).
- Sharma and S. and Kaiser, P. K., Update on VEGF TRAP-Eye Clinical Trials and Retinal. *Physician*, Nov./Dec. 2010, p. 1-6, <URL: <https://www.retinalphysician.com/issues/2010/nov-dec/update-on-vegfr-trap-eye-clinical-trials>>.
- Stewart et al., "Predicted biological activity of intravitreal VEGF Trap" *British Journal of Ophthalmology*, 2008, vol. 92, No. 5, p. 667-668.
- Stewart, "Aflibercept" *Nature Reviews: Drug Discovery* 11:269-270 (Apr. 1, 2012).
- Thurston, "Vascular endothelial growth factor and other signaling pathways in developmental and pathologic angiogenesis." *International Journal of Hematology* 80:7-20 (2004).
- Wachsberger, "VEGF trap in combination with radiotherapy improves tumor control in u87 glioblastoma." *Int. J. Radiation Oncology Biol Phys.* 67(5):1526-1537 (2007).
- ADSIS R&D Profile "Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap—Regeneron, VEGF Trap (RIR2), VEGF Trap-Eye." *Drugs R D*, 9(4):261-269 (2008).
- N/A "Materials from Jun. 2011 FDA Committee Mtg" (Jun. 17, 2011).
- N/A "Materials from Dec. 2011 FDA Committee Mtg" (Dec. 1, 2011).
- Vascular Endothelial Growth Factor Trap&#8208; 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].

(56)

## References Cited

## OTHER PUBLICATIONS

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

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).

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).

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

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://visioncareprofessional.com/emails/amupdate/index.asp?issue=42>.

Gomez-Manzano, “VEGF Trap induces antiglioma effect at different stages of disease.” *Neuro-Oncology*, 10:940-945 (Dec. 2008).

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

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&#8208;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).

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).

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](http://www.pslgroup.com/dg/23f2aa.htm), pp. 1-2 (Nov. 24, 2003).

Schmidt-Erfurth, “Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCIE Study” *Ophthalmology*, 118(5):831-839 (2010).

Schnichels, “Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells.” *Br. J. Ophthalmol.*, 97:917-923 (2013).

Simo and Hernandez, “Advances in Medical Treatment of Diabetic Retinopathy” *Diabetes Care*, 32(8):1556-1562 (Aug. 2009).

Spaide, “Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration.” *Am J Ophthalmology*, 143(4):679-680 (Apr. 2007).

Vascular Endothelial Growth Factor Trap&#8208;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] Note: May correspond to 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>)” Office Action dated Dec. 10, 2019 in U.S. Appl. No. 16/055,847.

Yancopoulos, “Clinical Application of Therapies Targeting VEGF.” *Cell* 143:13-16 (Oct. 1, 2010).

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

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 Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_01182013\_27424.1).

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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_01252011\_27433.1).

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) 11 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_01262012\_27428.1).

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 Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_01302013\_27423.1).

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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_02092010\_27442.1).

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) 11 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_02202012\_27427.1).

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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_03162010\_27441.1).

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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_04082011\_27432.1).

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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_04162010\_27440.1).

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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_06232011\_27431.1).

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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_07222010\_27439.1).

Updated Information from ClinicalTrials.gov archive History of Changes for Study: NCT01012973 Vascular Endothelial Growth



(56)

## References Cited

## OTHER PUBLICATIONS

- Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO)(GALILEO) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_08252010\_27438.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_08262010\_27437.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_09082010\_27436.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_09192011\_27430.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_10042010\_27435.1).  
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 Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_10232012\_27426.1).  
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 Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_10272013\_27422.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_11012010\_27434.1).  
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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_11132009\_27444.1).  
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) 10 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_11292011\_27429.1).  
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 Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_12182012\_27425.1).  
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) 12 pages, Latest version submitted Oct. 27, 2014 on ClinicalTrials.gov (NCT01012973\_12212010\_27443.1).  
Anonymous "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published Aug. 5, 2019).  
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 Health-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.  
DeVRIESE et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" *J. Am. Soc. Nephrol* (2001) 12:993-1000.  
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.  
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.  
Holash et al., "Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VegF" *Science* (Jun. 18, 1999) 284(5422):1994-1998.  
Korobelnik et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" *American Academy of Ophthalmology* (2014) 121(1):202-208.  
Mitchell, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" *Clinical Colorectal Cancer* (2013) 12(2):73-85.  
Noguera-Troise et al., "Blockade of D114 inhibits tumour growth by promoting nonproductive angiogenesis" *Nature* (Dec. 2006) 444:1032-1037.  
Rudge et al., "VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade" *PNAS* (Nov. 20, 2007) 104(47):18363-18370.  
Schmidt-Erfurth et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" *Ophthalmology* (2014) 121:193-201.  
Semeraro et al., "Aflibercept in wet AMD: specific role and optimal use" *Drug Design, Development and Therapy* (Aug. 2, 2013) 7:711-722.  
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.  
Thurston, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" *J. Anat.* (2002) 200:575-580.  
Xia et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" *Blood* (Jul. 1, 2003) 102(1):161-168.  
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).  
Do et al. "Results of a Phase 1 Study of Intravitreal VEGF Trap in Subjects with Diabetic Macular Edema: The CLEAR-IT DME Study" *ARVO Annual Meeting Abstract* (May 2007).

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.