terminate the agreement after making the first three additional payments. Upon commercialization of any antibody products discovered utilizing VelocImmune, the licensees will pay to Regeneron a mid-single-digit royalty on product sales.

Financial Results

Revenue

Regeneron's total revenue increased to $64.7 million in the fourth quarter of 2007 from $10.3 million in the same quarter of 2006 and to $125.0 million for the full year 2007 from $63.4 million for the same period of 2006. Contract research and development revenue in the first three quarters of 2007 and the full-year 2006 principally related to the Company's aflibercept collaboration with sanofi-aventis in cancer indications. In the fourth quarter of 2007, the Company also recognized contract research and development revenue from the Company's VEGF Trap-Eye collaboration with Bayer HealthCare and its new collaboration with sanofi-aventis to discover, develop, and commercialize fully human monoclonal antibodies. Contract manufacturing revenue in 2006 related to Regeneron's long-term manufacturing agreement with Merck & Co., Inc., which expired in October 2006. Technology licensing revenue in 2007 related to the Company's license agreements with AstraZeneca and Astellas.

Regeneron recognized contract research and development revenue of $12.6 million in the fourth quarter of 2007 and $47.1 million for the full year 2007 related to the Company's aflibercept collaboration with sanofi-aventis, compared with $9.1 million and $47.8 million, respectively, for the same periods of 2006. Contract research and development revenue from the collaboration consisted of reimbursement of aflibercept development expenses incurred by the Company plus recognition of amounts related to $105.0 million of previously received and deferred non-refundable, up-front payments. Reimbursement of expenses increased to $10.5 million in the fourth quarter of 2007 and to $38.3 million for the full year 2007 from $6.8 million and $36.4 million, respectively, in the comparable periods of 2006, principally due to higher preclinical and clinical development costs and, in the fourth quarter of 2007, higher costs related to the Company's manufacture of aflibercept clinical supplies. With respect to the $105.0 million of up-front payments from sanofi-aventis, $2.1 million was recognized in the fourth quarter of 2007 compared to $2.2 million in the same quarter of 2006, and $8.8 million was recognized in the full year 2007 compared to $11.4 million in the same period of 2006.

Sanofi-aventis also incurs aflibercept development expenses directly and these expenses are increasing because of the growing number of clinical trials sanofi-aventis is overseeing in the aflibercept oncology program. During the term of the aflibercept collaboration, sanofi-aventis pays 100 percent of agreed-upon aflibercept development expenses incurred by both companies. Following commercialization of an aflibercept product, Regeneron, from its 50 percent share of aflibercept profits, will reimburse sanofi-aventis for 50 percent of aflibercept development expenses previously paid by sanofi-aventis.

In connection with the Company's VEGF Trap-Eye collaboration with Bayer HealthCare, the Company received a $75.0 million non-refundable, up-front payment in October 2006 and a $20.0 million milestone payment in August 2007. Through September 30, 2007, all payments received from Bayer HealthCare, including the up-front and milestone payments and cost-sharing reimbursements, were fully deferred and included in deferred revenue. In the fourth quarter of 2007, the Company commenced recognizing previously deferred payments from Bayer HealthCare and cost-sharing of the Company's and Bayer HealthCare's 2007 VEGF Trap-Eye development expenses in the Company's Statement of Operations through a cumulative catch-up. The $75.0 million non-refundable, up-front license payment and $20.0 million milestone payment are being recognized as contract research and development revenue over the related estimated performance period in accordance with Staff Accounting Bulletin No. 104, Revenue Recognition (SAB 104) and Emerging Issues Task Force 00-21, Accounting for Revenue Arrangements with Multiple Deliverables (EITF 00-21). In periods when the Company recognizes VEGF Trap-Eye development expenses that it incurs under the collaboration, the Company also recognizes, as contract research and development revenue, the portion of those VEGF Trap-Eye development expenses that are reimbursable from Bayer HealthCare. In periods when Bayer HealthCare incurs agreed upon VEGF Trap-Eye development expenses that benefit the collaboration and Regeneron, the Company also recognizes, as additional research and development expense, the portion of Bayer HealthCare's VEGF Trap-Eye development expenses that the Company is obligated to reimburse.

In the fourth quarter of 2007, the Company recorded a cumulative catch-up of $35.9 million of contract research and development revenue from Bayer HealthCare, consisting of (i) $15.9 million related to the $75.0 million up-front licensing payment and the $20.0 million milestone payment and (ii) $20.0 million related to the portion of the Company's 2007 VEGF Trap-Eye development expenses that is reimbursable from Bayer HealthCare. In addition, in the fourth quarter of 2007, the Company recorded a cumulative catch-up of $10.6 million of additional research and development expense related to the portion of Bayer HealthCare's 2007 VEGF Trap-Eye development expenses that the Company was obligated to reimburse.

In connection with the Company's antibody collaboration with sanofi-aventis, the Company recognized $4.6 million of contract research and development revenue in the fourth quarter of 2007, which consisted of $3.0 million for reimbursement of the Company's expenses under the collaboration's discovery agreement, $0.7 million for reimbursement of the Company's REGN88 development expenses, and $0.9 million related to the $85.0 million non-refundable, up-front payment, which was deferred upon receipt in December 2007. Contract research and development revenue in connection with the antibody collaboration with sanofi-aventis is being recognized in accordance with SAB 104 and EITF 00-21.

Contract research and development revenue also includes $1.0 million in the fourth quarter of 2007 and $5.5 million for the full year 2007, compared to $0.4 million and $0.5 million, respectively, for the same periods of 2006, in connection with the Company's five-year grant from the National Institutes of Health (NIH), which was awarded to the Company in September 2006 as part of the NIH's Knockout Mouse Project.

In connection with the Company's license agreements with AstraZeneca and Astellas, both of the $20.0 million non-refundable, up-front payments received in February and April 2007, respectively, were deferred and are being recognized as revenue ratably over approximately the first year of each agreement. In the fourth quarter and for the full year 2007, the Company recognized $10.0 million and $28.4 million, respectively, of technology licensing revenue related to these agreements.

Expenses

Total operating expenses for the fourth quarter of 2007 were $76.3 million, 74 percent higher than the same period in 2006, and $239.5 million for the full year 2007, 40 percent higher than for the same period of 2006. Operating expenses included non-cash compensation expense related to employee stock option awards (Stock Option Expense) of $7.5 million in the fourth quarter of 2007 and $28.0 million for the full year 2007, compared

with $5.1 million and $18.4 million, respectively, for the same periods of 2006. The increase in total Stock Option Expense in 2007 was primarily due to the higher fair market value of the Company's Common Stock on the date of annual employee option grants made by the Company in December 2006 in comparison to the fair market value of the Company's Common Stock on the dates of annual employee option grants made in recent prior years.

Research and development (R&D) expenses increased to $64.8 million in the fourth quarter of 2007 from $35.8 million in the comparable quarter of 2006, and to $201.6 million for the full year 2007 from $137.1 million for the same period of 2006. In addition to the impact of Stock Option Expense, as described above, in 2007, the Company incurred higher R&D costs primarily related to additional R&D headcount, clinical development costs for the VEGF Trap-Eye and ARCALYST, research and preclinical development costs for new antibody candidates, and costs to manufacture clinical supplies of ARCALYST and REGN88. Also, as described above, in the fourth quarter of 2007, the Company recorded a cumulative catch-up of $10.6 million of additional research and development expense related to the Company's VEGF Trap-Eye collaboration with Bayer HealthCare.

General and administrative (G&A) expenses increased to $11.4 million in the fourth quarter of 2007 from $7.6 million in the comparable quarter of 2006, and to $37.9 million in the full year 2007 from $25.9 million in the same period of 2006. In addition to the impact of Stock Option Expense, as described above, in 2007, the Company incurred higher compensation expense due, in part, to additional headcount, higher recruitment and related costs associated with expanding the Company's headcount in 2007, and higher fees for various professional services.

Other Income

Investment income decreased to $1.5 million in the fourth quarter of 2007 from $5.5 million in the comparable quarter of 2006, and increased to $20.9 million for the full year 2007 from $16.5 million for the same period of 2006. In the fourth quarter and for the full year 2007, the Company recognized $5.1 million and $5.9 million, respectively, in charges related to certain marketable securities that were determined to be other-than-temporarily impaired in value. For the full-year 2007, the increase in investment income resulted primarily from higher balances of cash and marketable securities due, in part, to the up-front payment received from Bayer HealthCare in October 2006 and the receipt of $174.6 million in net proceeds from the November 2006 public offering of 7.6 million shares of the Company's Common Stock, partly offset by the impairment charges previously described.

About Regeneron Pharmaceuticals

Regeneron is a biopharmaceutical company that discovers, develops, and intends to commercialize therapeutic medicines for the treatment of serious medical conditions. Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, and inflammatory diseases, and has preclinical programs in other diseases and disorders.

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of our drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict our ability to continue to develop or commercialize our drug candidates, competing drugs that are superior to our product candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including our agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2006 and Form 10-Q for the quarter ended September 30, 2007. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

REGENERON PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS (Unaudited)
(In thousands)

	December 31, 2007	December 31, 2006	
ASSETS			
Cash, restricted cash, and marketable securities	$846,279	$522,859	
Receivables	18,320	7,493	
Property, plant, and equipment, net	58,304	49,353	
Other assets	13,355	5,385	
Total assets	$936,258	$585,090	
LIABILITIES AND STOCKHOLDERS' EQUITY			
Accounts payable and accrued expenses	$39,232	$21,471	
Deferred revenue	236,759	146,995	
Notes payable	200,000	200,000	
Stockholders' equity	460,267	216,624	
Total liabilities and			

stockholders' equity	$936,258 $585,090

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF OPERATIONS (Unaudited)
(In thousands, except per share data)

	For the three months ended December 31,		For the year ended December 31,	
	2007	2006	2007	2006
Revenues				
Contract research and development	$54,730	$10,110	$96,603	$51,136
Contract manufacturing		236		12,311
Technology licensing	10,000		28,421	
	64,730	10,346	125,024	63,447
Expenses				
Research and development	64,825	35,774	201,613	137,064
Contract manufacturing		430		8,146
General and administrative	11,439	7,628	37,865	25,892
	76,264	43,832	239,478	171,102
Loss from operations	(11,534)	(33,486)	(114,454)	(107,655)
Other income (expense)				
Investment income	1,473	5,525	20,897	16,548
Interest expense	(3,010)	(3,010)	(12,043)	(12,043)
	(1,537)	2,515	8,854	4,505
Net loss before cumulative effect of a change in accounting principle	(13,071)	(30,971)	(105,600)	(103,150)
Cumulative effect of adopting Statement of Financial Accounting Standards No. 123R ("SFAS 123R")				813
Net loss	$(13,071)	$(30,971)	$(105,600)	$(102,337)
Net loss per share amounts, basic and diluted:				
Net loss before cumulative effect of a change in accounting principle	$(0.19)	$(0.51)	$(1.59)	$(1.78)
Cumulative effect of adopting SFAS 123R				0.01
Net loss	$(0.19)	$(0.51)	$(1.59)	$(1.77)
Weighted average shares				

outstanding, basic and diluted	67,754	61,229	66,334	57,970

CONTACT: Investor Relations
Charles Poole, 914-345-7640
charles.poole@regeneron.com
OR
Media Relations
Laura Lindsay, 914-345-7800
laura.lindsay@regeneron.com
OR
Kimberly Chen, 212-845-5634
kchen@biosector2.com

SOURCE: Regeneron Pharmaceuticals, Inc.

REGENERON

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

April 28, 2008

Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular DegenerationTARRYTOWN, N.Y. & LEVERKUSEN, Germany--(BUSINESS WIRE)--April 28, 2008--Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare AG today announced that VEGF Trap-Eye dosed on a PRN (as-needed) dosing schedule maintained the statistically significant gain in visual acuity achieved after an initial, 12-week, fixed-dosing phase of a Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD). A full analysis of the 32-week results of the Phase 2 study will be presented today at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, Florida. The data being reported at the meeting are available on the Regeneron website (www.regeneron.com on the Investor Relations page, under the Presentations heading).

Study results showed that across all dose groups in the study population, the 6.6 mean letter gain in visual acuity achieved versus baseline at the week 16 evaluation visit, following 12 weeks of fixed dosing, was maintained out to week 32 (a 6.7 mean letter gain versus baseline; p less than 0.0001) using a PRN dosing schedule (where dosing frequency was determined by the physician's assessment of pre-specified criteria). The decrease in retinal thickness, an anatomical measure of treatment effect achieved with a fixed-dose schedule was also maintained for all dose groups combined at week 32 (a 137 micron mean decrease versus baseline, p less than0.0001).

In this double-masked, prospective, randomized, multi-center Phase 2 trial, 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye for 12 weeks and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dose phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity. These data represent the week 32 analysis from the 52-week study, which is continuing to follow patients.

Patients receiving monthly doses of VEGF Trap-Eye, either 0.5 or 2.0 mg, for 12 weeks followed by PRN dosing thereafter achieved mean improvements in visual acuity of 8.0 (p less than0.01 versus baseline) and 10.1 letters (p less than0.0001 versus baseline), respectively, and mean decreases in retinal thickness of 141 (p less than0.0001 versus baseline) and 162 microns (p less than0.0001 versus baseline) at week 32, respectively. While PRN dosing also maintained the improvements in retinal thickness and visual acuity achieved versus baseline following a fixed dosing regimen utilizing quarterly dosing at baseline and week 12, the results achieved with a quarterly fixed dosing regimen were generally not as robust as obtained with initial fixed monthly dosing.

VEGF Trap-Eye was generally safe and well tolerated and there were no drug-related serious adverse events. There was one reported case of culture-negative endophthalmitis/uveitis in the study eye, which was deemed not to be drug-related. The most common adverse events were those typically associated with intravitreal injections.

After the last fixed-dose administration at week 12, patients from all dose groups combined required, on average, only one additional injection over the following 20 weeks to maintain the visual acuity gain established during the fixed-dosing period. Notably, 55 percent of the patients who received 2.0 mg monthly for 12 weeks did not require any additional treatment throughout the next 20-week PRN dosing period. Moreover, 97 percent of the patients who received 2.0 mg monthly for 12 weeks did not require re-dosing at the week 16 evaluation visit, indicating that an 8-week dosing schedule may be feasible.

"Due to its high affinity for all isoforms of VEGF-A and PlGF, potent mediators of blood vessel overgrowth in wet AMD, as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly, especially on a chronic basis, without compromising visual acuity," stated Quan Dong Nguyen, M.D., M.Sc.,* Assistant Professor of Ophthalmology, Wilmer Ophthalmological Institute, the Johns Hopkins University School of Medicine, Baltimore, MD and a primary investigator in the Phase 2 study. "These emerging Phase 2 clinical data seem to support the concept of durability of VEGF Trap-Eye."

In this study, treatment with VEGF Trap-Eye was associated with a reduction in the size of the choroidal neovascular membrane (CNV), the lesion that is the underlying cause of vision loss due to wet AMD. Patients initially treated with a 0.5 mg or 2.0 mg monthly fixed dose for 12 weeks, followed by PRN dosing thereafter, experienced 1.55 mm(2) and 2.52 mm(2) reductions in mean CNV size at 24 weeks (the most recently available analysis from the independent reading center) versus baseline, respectively. Patients treated initially with fixed quarterly dosing also experienced an overall reduction in CNV size.

"Regression in CNV size is generally not seen when treating wet AMD patients. The reduction in CNV size achieved thus far with VEGF Trap-Eye treatment highlights the potential clinical utility of this investigational treatment in patients suffering from this devastating condition," stated Jason Slakter, M.D., Clinical Professor of Ophthalmology, New York University School of Medicine, New York.

"These study results further increase our confidence in the design of our Phase 3 clinical program for VEGF Trap-Eye in wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "These studies are evaluating the clinical efficacy and safety of VEGF Trap-Eye, using a monthly loading dose of 0.5 mg or 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of 0.5 mg monthly, 2.0 mg monthly, or 2.0 mg every eight weeks. In the second year of the studies, all patients will be dosed on a PRN basis."

About the Phase 3 Program in Wet AMD

Regeneron and Bayer HealthCare initiated a Phase 3 global development program for VEGF Trap-Eye in wet AMD in August 2007. In two Phase 3 trials, the companies are evaluating VEGF Trap-Eye using four- and eight-week dosing intervals in direct comparison with ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.) administered every four weeks according to its label during the first year of the studies. PRN dosing will be evaluated during the second year of each study. The VIEW1 study is currently enrolling patients in the United States and Canada. The VIEW2 study has recently been initiated and will enroll patients in up to 200 centers in Europe, Asia Pacific, Japan, and Latin America. The companies are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, diabetic eye diseases, and other eye diseases and disorders. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. The VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Blockade of VEGF, which can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD and a VEGF inhibitor, ranibizumab, has been approved for treatment of patients with this condition.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (nonexudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About Regeneron Pharmaceuticals, Inc.

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, and inflammatory diseases, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2007. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

* The assessment made by Dr. Nguyen does not necessarily imply endorsement by the Johns Hopkins University, the Johns Hopkins Hospital, or the Johns Hopkins Medical Institutions.

CONTACT: Regeneron Pharmaceuticals, Inc.
Investor Relations, 914-345-7640
invest@regeneron.com
or
Corporate Communications
Laura Lindsay, 914-345-7800
laura.lindsay@regeneron.com
or
Media Relations
Kimberly Chen, 212-845-5634
kchen@biosector2.com

SOURCE: Regeneron Pharmaceuticals, Inc.

REGENERON

Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration

August 19, 2008

Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2 Study in Patients with Age-related Macular Degeneration**Tarrytown, NY and Leverkusen, Germany (August 19, 2008)** – Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) and Bayer HealthCare AG today announced that patients with wet age-related macular degeneration (AMD) receiving VEGF Trap-Eye in a Phase 2 extension study on a PRN (as needed) dosing schedule continued to show highly significant improvements at 52 weeks in the primary and key secondary endpoints of retinal thickness (an anatomic measure of treatment effect) and vision gain. The 12-week primary endpoint results from the fixed-dosing period of the study were presented at the 2007 Retina Society conference in September 2007. The 32-week results of the Phase 2 study were presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, Florida in April 2008. A full analysis of the 52-week results of the Phase 2 study will be presented at the 2008 meeting of the Retina Society on September 26-28, 2008 in Scottsdale, Arizona.

In this double-masked, prospective, randomized, multi-center Phase 2 trial, 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity. These data represent the final one-year analysis from the 52-week study.

Patients receiving four monthly doses of VEGF Trap-Eye, either 2.0 or 0.5 mg, for 12 weeks followed by PRN dosing thereafter, achieved mean improvements in visual acuity versus baseline of 9.0 letters ($p<0.0001$) and 5.4 letters ($p=0.085$), respectively, and mean decreases in retinal thickness versus baseline of 143 microns ($p<0.0001$) and 125 microns ($p<0.0001$) at week 52, respectively. During the subsequent PRN dosing phase, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.

For all dose cohorts combined, there was a 5.3 mean letter gain in visual acuity versus baseline at the week 52 evaluation visit ($p<0.0001$). The mean decrease in retinal thickness for all dose groups combined at week 52 was 130 microns versus baseline ($p<0.0001$). During the week 12 to week 52 PRN dosing period, patients from all dose groups combined received, on average, only two additional injections.

VEGF Trap-Eye was generally well tolerated and there were no drug-related serious adverse events. There was one reported case of culture-negative endophthalmitis/uveitis in the study eye and one arterial thrombotic event, neither of which was deemed to be drug-related. The most common adverse events were those typically associated with intravitreal injections.

"Based upon retinal physicians' feedback, there remains a significant unmet medical need for a treatment for wet AMD that can reliably improve visual acuity over time without the need for monthly intravitreal injections," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "We are excited about these study findings and the potential for VEGF Trap-Eye to fulfill this need pending the results of our ongoing Phase 3 clinical studies."

"The 52-week results underline that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision," said Dr. Kemal Malik, member of the Bayer HealthCare Executive Committee responsible for product development. "The further development of this compound is important for millions of people worldwide who suffer from this devastating ocular disease."

About the Phase 3 Program in Wet AMD

Regeneron and Bayer HealthCare initiated a Phase 3 global development program for VEGF Trap-Eye in wet AMD in August 2007. In two Phase 3 trials, VIEW 1 and VIEW 2 (**V**EGF Trap-Eye: **I**nvestigation of **E**fficacy and Safety in **W**et Age-related Macular Degeneration), the companies are evaluating VEGF Trap-Eye dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, or 2 mg every 8 weeks (following three monthly doses) in direct comparison with ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.) administered 0.5 mg every four weeks according to its U.S. label during the first year of the studies. PRN dosing will be evaluated during the second year of each study. The VIEW1 study (http://www.regeneron.com /vegftrap_eye.html) is currently enrolling patients in the United States and Canada and the VIEW2 study (www.view2study.com) is currently enrolling patients in Europe, Asia Pacific, Japan, and Latin America. The companies are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, diabetic eye diseases, and other eye diseases and disorders. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. The VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Blockade of VEGF, which can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD.

About Wet AMD
Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (nonexudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About Regeneron Pharmaceuticals, Inc.
Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, and inflammatory diseases, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statement
This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2007 and Form 10-Q for the quarter ending June 30, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

Contact Information:

Regeneron Pharmaceuticals, Inc.
Investor Relations
914-345-7640
invest@regeneron.com

Laura Lindsay
Corporate Communications
914-345-7800
laura.lindsay@regeneron.com

Lauren Tortorete
Media Relations
212-845-5609
ltortorete@biosector2.com

Bayer HealthCare
Astrid Kranz
+49 30 468-12057
astrid.kranz@bayerhealthcare.com

REGENERON

Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results

February 26, 2009
Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating ResultsTARRYTOWN, N.Y.--(BUSINESS WIRE)--Feb. 26, 2009-- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced financial and operating results for the full year and fourth quarter 2008. The Company reported a net loss of $82.7 million, or $1.05 per share (basic and diluted), for the year ended December 31, 2008 compared with a net loss of $105.6 million, or $1.59 per share (basic and diluted), for the same period in 2007. The Company reported a net loss of $31.5 million, or $0.40 per share (basic and diluted), for the fourth quarter of 2008 compared with a net loss of $13.1 million, or $0.19 per share (basic and diluted), for the fourth quarter of 2007. In the fourth quarter of 2007, in connection with the Company's VEGF Trap-Eye collaboration with Bayer HealthCare, the Company recognized a cumulative catch-up of revenue and expenses that reduced the net loss for the quarter by $25.3 million, as described below.

At December 31, 2008, cash, restricted cash, and marketable securities totaled $527.5 million compared with $846.3 million at December 31, 2007. During 2008, the Company retired the full $200 million of its 5.5 percent Convertible Senior Subordinated Notes.

Current Business Highlights

ARCALYST® (rilonacept) – Inflammatory Diseases

The Company shipped $10.7 million of ARCALYST® (rilonacept) Injection for Subcutaneous Use to its distributors in 2008. In February 2008, the Company received marketing approval from the U.S. Food and Drug Administration (FDA) for ARCALYST for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. ARCALYST, an interleukin-1 (IL-1) blocker, is the only therapy approved in the United States for patients with CAPS, a group of rare, inherited, auto-inflammatory conditions characterized by life-long, recurrent symptoms of rash, fever/chills, joint pain, eye redness/pain, and fatigue. Intermittent, disruptive exacerbations or flares can be triggered at any time by exposure to cooling temperatures, stress, exercise, or other unknown stimuli.

In March 2008, ARCALYST became available for prescription in the United States, and the Company transitioned the patients who participated in the CAPS pivotal study from clinical study drug to commercial supplies. The Company currently projects shipments of ARCALYST to its distributors to total approximately $20-24 million in 2009.

The Company is in the process of initiating a Phase 3 clinical development program with ARCALYST for the treatment of gout. Two Phase 3 clinical trials will evaluate ARCALYST versus placebo for the prevention of gout flares in patients initiating urate-lowering drug therapy. The Company plans to initiate a Phase 3 clinical trial of ARCALYST for acute gout that will evaluate treatment with ARCALYST alone versus ARCALYST in combination with a non-steroidal anti-inflammatory drug (NSAID) versus an NSAID alone. The Phase 3 clinical development program will also include a separate safety study.

Aflibercept (VEGF Trap) – Oncology

Regeneron and collaborator sanofi-aventis are enrolling patients in four Phase 3 trials that combine aflibercept, an anti-angiogenesis agent, with standard chemotherapy regimens for the treatment of cancer. One trial is evaluating aflibercept as a 2nd line treatment for metastatic colorectal cancer (the VELOUR study) in combination with FOLFIRI (folinic acid (leucovorin), 5-fluorouracil, and irinotecan). A second trial is evaluating aflibercept as a 1st line treatment for metastatic pancreatic cancer in combination with gemcitabine (the VANILLA study). A third trial is evaluating aflibercept as a 1st line treatment for metastatic androgen- independent prostate cancer in combination with docetaxel/prednisone (the VENICE study). The fourth trial is evaluating aflibercept as a 2nd line treatment for metastatic non-small cell lung cancer in combination with docetaxel (the VITAL study). All four trials are studying the current standard of chemotherapy care for the cancer being studied with and without aflibercept. Each of the four Phase 3 trials is over one-third enrolled, and initial data from the Phase 3 program is expected in 2010. In addition, a Phase 2 study of aflibercept in 1st line metastatic colorectal cancer in combination with folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin (the AFFIRM study) began recruiting patients in January 2009.

Aflibercept is also being studied in a Phase 2 single-agent study in advanced ovarian cancer (AOC) patients with symptomatic malignant ascites (SMA). This trial is now fully enrolled and we expect to have initial data from this trial by mid 2009.

VEGF Trap-Eye – Ophthalmologic Diseases

VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications. Regeneron and collaborator Bayer HealthCare are testing VEGF Trap-Eye in a Phase 3 program in patients with the neovascular form of age-related macular degeneration (wet AMD). Regeneron and Bayer HealthCare also initiated a Phase 2 study of VEGF Trap-Eye in patients with diabetic macular edema (DME) in late 2008.

The Phase 3 trials in wet AMD, known as VIEW 1 and VIEW 2 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), are comparing VEGF Trap-Eye and ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.), an anti-angiogenic agent approved for use in wet AMD. VIEW 1 is being conducted in North America and VIEW 2 is being conducted in Europe, Asia Pacific, Japan, and Latin America. The VIEW 1 and VIEW 2 trials are both evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye compared with ranibizumab

dosed according to its U.S. label every four weeks over the first year. As needed dosing (PRN) with both agents will be evaluated in the second year of the studies. The VIEW 1 and VIEW 2 trials are expected to complete enrollment in 2009, and initial data are expected in late 2010.

The recently initiated Phase 2 DME study, known as the DA VINCI study, is a double-masked, randomized, controlled trial that is evaluating four different VEGF Trap-Eye regimens versus laser treatment. The study will be enrolling approximately 200 patients in the U.S., Canada, European Union, and Australia. The patients in the study will be treated for 52 weeks followed up by six additional months of safety evaluation. The primary efficacy endpoint is the change in best corrected visual acuity (BCVA) from baseline to week 24.

Monoclonal Antibodies

Regeneron and sanofi-aventis are collaborating on the discovery, development, and commercialization of fully human monoclonal antibodies generated by Regeneron using its *VelocImmune®* technology. The first therapeutic antibodies to enter clinical development under the collaboration are REGN88, an antibody to the interleukin-6 receptor (IL-6R) that is being evaluated in rheumatoid arthritis, and REGN475, an antibody to Nerve Growth Factor (NGF) that is being developed for the treatment of pain. In addition, a Phase 1 trial is in the process of being initiated for REGN421, an antibody to Delta-like ligand-4 (Dll4) that will be evaluated in oncology in patients with advanced malignancies. Over the course of the next several years, the Company and sanofi-aventis plan to advance an average of two to three new fully human antibodies into clinical development each year.

Financial Results

Revenues

Total revenues decreased to $55.8 million in the fourth quarter of 2008 from $64.7 million in the same quarter of 2007 and increased to $238.5 million for the full year 2008 from $125.0 million for the same period of 2007. The Company's revenue was comprised of contract research and development revenue, technology licensing revenue, and net product sales.

Contract Research and Development Revenue

Contract research and development revenue relates primarily to the Company's aflibercept and antibody collaborations with sanofi-aventis and the Company's VEGF Trap-Eye collaboration with Bayer HealthCare. Contract research and development revenue for the three months and years ended December 31, 2008 and 2007, consisted of the following:

	Three months ended December 31,		**Year ended December 31,**	
(In millions)	**2008**	**2007**	**2008**	**2007**
Contract research & development revenue				
Sanofi-aventis	$37.6	$17.2	$154.0	$51.7
Bayer HealthCare	3.0	35.9	31.2	35.9
Other	1.7	1.6	7.0	9.0
Total contract research & development revenue	$42.3	$54.7	$192.2	$96.6

For the three months and years ended December 31, 2008 and 2007, contract research and development revenue from sanofi-aventis consisted of the following:

	Three months ended December 31,		**Year ended December 31,**	
(In millions)	**2008**	**2007**	**2008**	**2007**
Aflibercept:				
Regeneron expense reimbursement	$6.3	$10.5	$35.6	$38.3
Recognition of deferred revenue related to up-front payments	2.5	2.1	8.8	8.8
Total aflibercept	8.8	12.6	44.4	47.1
Antibody:				
Regeneron expense reimbursement	25.5	3.7	97.9	3.7
Recognition of deferred revenue related to up-front payment	2.6	0.9	10.5	0.9
Other	0.7	___	1.2	___
Total antibody	28.8	4.6	109.6	4.6
Total sanofi-aventis contract research & development revenue	$37.6	$17.2	$154.0	$51.7

Sanofi-aventis' reimbursement of Regeneron's aflibercept expenses decreased for the three months and year ended December 31, 2008, compared to the same periods in 2007, primarily due to lower costs related to manufacturing aflibercept clinical supplies.

Revenue under the antibody collaboration increased for the three months and year ended December 31, 2008 compared to the same periods in 2007 due to the initiation of the collaboration in November 2007.

For the three months and years ended December 31, 2008 and 2007, contract research and development revenue from Bayer HealthCare consisted of the following:

	Three months ended December 31,		Year ended December 31,	
(In millions)	**2008**	**2007**	**2008**	**2007**
Cost-sharing of Regeneron VEGF Trap-Eye development expenses	$0.5	$20.0	$18.8	$20.0
Recognition of deferred revenue related to up-front and milestone payments	2.5	15.9	12.4	15.9
Total Bayer HealthCare contract research & development revenue	$3.0	$35.9	$31.2	$35.9

In connection with the Company's VEGF Trap-Eye collaboration with Bayer HealthCare, the Company received a $75.0 million non-refundable, up-front payment in October 2006 and a $20.0 million milestone payment in August 2007. Through September 30, 2007 all payments received from Bayer HealthCare, including the up-front and milestone payments and cost sharing reimbursements, were fully deferred and included in deferred revenue. In the fourth quarter of 2007, the Company commenced recognizing previously deferred payments from Bayer HealthCare and cost sharing of the Company's VEGF Trap-Eye development expenses in the Company's Statement of Operations through a cumulative catch-up. The $75.0 million non-refundable, up-front license payment and $20.0 million milestone payment are being recognized as contract research and development revenue over the related estimated performance period. In periods when the Company recognizes VEGF Trap-Eye development expenses that it incurs under the collaboration, the Company also recognizes, as contract research and development revenue, the portion of those VEGF Trap-Eye development expenses that is reimbursable from Bayer HealthCare. In periods when Bayer HealthCare incurs agreed upon VEGF Trap-Eye development expenses that benefit the collaboration and Regeneron, the Company also recognizes, as additional research and development expense, the portion of Bayer HealthCare's VEGF Trap-Eye development expenses that the Company is obligated to reimburse.

In the fourth quarter of 2007, the Company recorded a cumulative catch-up of $35.9 million of contract research and development revenue from Bayer HealthCare. In addition, in the fourth quarter of 2007, the Company recorded a cumulative catch-up of $10.6 million of additional research and development expense related to the portion of Bayer HealthCare's 2007 VEGF Trap-Eye development expenses that the Company was obligated to reimburse.

Under the terms of the Bayer HealthCare collaboration, in 2008, the first $70.0 million of agreed-upon VEGF Trap-Eye development expenses incurred by the Company and Bayer HealthCare under a global development plan were shared equally, and the Company was solely responsible for up to the next $30.0 million. During the fourth quarter of 2008, Regeneron was solely responsible for most of the collaboration's VEGF Trap-Eye development expenses. As a result, in the fourth quarter of 2008, the portion of the Company's VEGF Trap-Eye development expenses that were reimbursable from Bayer HealthCare, and recognized as contract research and development revenue, amounted to only $0.5 million.

Technology Licensing Revenue

Regeneron has entered into non-exclusive license agreements with AstraZeneca and Astellas that allow those companies to utilize *VelocImmune®* technology in their internal research programs to discover human monoclonal antibodies. Each company made $20.0 million annual, non-refundable payments in each of 2007 and 2008 and agreed to make up to four additional annual payments of $20.0 million, subject to the ability to terminate their agreements after making two such additional payments. Upon receipt, these payments are deferred and are recognized as revenue ratably over approximately the ensuing year of each agreement. Regeneron will also receive a mid-single-digit royalty on sales of any antibodies discovered utilizing *VelocImmune*.

Net Product Sales

The Company shipped $10.7 million of ARCALYST® (rilonacept) to its distributors in 2008 and recorded $3.5 million and $6.3 million in product sales revenue for the three months and year ended December 31, 2008. Revenue and deferred revenue from product sales are recorded net of applicable provisions for prompt pay discounts, product returns, estimated rebates payable under governmental programs (including Medicaid), distributor fees, and other sales-related costs. At December 31, 2008, $4.0 million of ARCALYST net product sales was included in deferred revenue in the Company's financial statements.

Expenses

Total operating expenses for the fourth quarter of 2008 were $90.4 million, 19 percent higher than the same period in 2007, and $328.3 million for the full year 2008, 37 percent higher than for the same period of 2007. Average headcount increased to 903 for the fourth quarter of 2008 compared to 665 for the same period in 2007 and increased to 810 for the full year 2008 from 627 for the full year 2007, due primarily to the Company's expanding research and development activities principally in connection with the Company's antibody collaboration with sanofi-aventis.

Operating expenses included non-cash compensation expense related to employee stock option and restricted stock awards of $7.8 million in the fourth quarter of 2008 and $32.5 million for the full year of 2008, compared with $7.5 million and $28.1 million, respectively, for the same periods of 2007.

Research and development (R&D) expenses increased to $76.3 million in the fourth quarter of 2008 from $64.8 million in the comparable quarter of 2007, and to $278.0 million for the full year 2008 from $201.6 million for the same period of 2007. In the fourth quarter and for the full year of 2008, the Company incurred higher R&D costs primarily related to additional R&D headcount, clinical development costs for ARCALYST and REGN88, research and preclinical development costs associated with our antibody programs, and facility-related costs to support the Company's expanded R&D activities. In addition, for the full year of 2008, the Company incurred higher R&D costs related to clinical development of VEGF Trap-Eye and manufacturing supplies of our drug product candidates, especially our monoclonal antibodies. Also, as described above, commencing in the fourth quarter of 2007, the Company began recognizing as additional R&D expense, the portion of Bayer HealthCare's VEGF Trap-Eye development expenses that the Company is obligated to reimburse.

Selling, general, and administrative (SG&A) expenses increased to $13.5 million in the fourth quarter of 2008 from $11.4 million in the comparable quarter of 2007, and to $49.4 million for the full year 2008 from $37.9 million for the full year 2007. In 2008, the Company incurred $5.2 million of selling expenses related to ARCALYST® (rilonacept) for the treatment of CAPS. In addition, the Company incurred higher compensation expense and recruitment costs associated with expanding the Company's SG&A headcount, higher professional fees related to various general corporate matters, and higher SG&A facility related costs.

Other Income and Expense

Investment income increased to $2.6 million in the fourth quarter of 2008 from $1.5 million in the comparable quarter of 2007, and decreased to $18.2 million for the full year 2008 from $20.9 million for the full year 2007. For the full year 2008, investment income decreased primarily due to lower yields on our cash and marketable securities. The Company recognized charges of $0.2 million and $5.1 million for the fourth quarters of 2008 and 2007, respectively, and $2.5 million and $5.9 million for the full year 2008 and 2007, respectively, related to certain marketable securities that were determined to be other-than-temporarily impaired. For the full year 2008, these charges were partially offset by realized gains of $1.2 million on sales of marketable securities during the year.

During the second and third quarters of 2008, the Company repurchased $82.5 million in principal amount of its 5.5 percent Convertible Senior Subordinated Notes. In connection with the repurchased notes, the Company recognized a $0.9 million loss on early extinguishment of debt. The remaining $117.5 million of these notes were repaid in full upon their maturity in October 2008.

Income Tax Expense

In the fourth quarter of 2008, the Company recognized a $0.7 million income tax benefit, resulting from a provision in the Housing Assistance Tax Act of 2008 that allowed the Company to claim a refund for certain unused pre-2006 research tax credits. For the full year 2008, income tax expense was $2.4 million and consisted primarily of alternative minimum tax, which resulted from the utilization of certain net operating loss carry-forwards, that would otherwise have expired over the next several years, to offset income for tax purposes.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

REGENERON PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS (Unaudited)
(In thousands)

	December 31, 2008	**December 31, 2007**
ASSETS		
Cash, restricted cash, and marketable securities	$527,461	$846,279
Receivables	35,212	18,320
Property, plant, and equipment, net	87,853	58,304
Other assets	19,512	13,355
Total assets	$670,038	$936,258
LIABILITIES AND STOCKHOLDERS' EQUITY		
Accounts payable, accrued expenses, and other liabilities	$41,261	$39,232
Deferred revenue	209,925	236,759
Notes payable		200,000
Stockholders' equity	418,852	460,267
Total liabilities and stockholders' equity	$670,038	$936,258

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF OPERATIONS (Unaudited)
(In thousands, except per share data)

	For the three months ended December 31,		For the year ended December 31,	
	2008	2007	2008	2007
Revenues				
Contract research and development	$42,294	$54,730	$192,208	$96,603
Technology licensing	10,000	10,000	40,000	28,421
Net product sales	3,543		6,249	
	55,837	64,730	238,457	125,024
Expenses				
Research and development	76,314	64,825	278,016	201,613
Selling, general, and administrative	13,491	11,439	49,348	37,865
Cost of goods sold	631		923	
	90,436	76,264	328,287	239,478
Loss from operations	(34,599)	(11,534)	(89,830)	(114,454)
Other income (expense)				
Investment income	2,648	1,473	18,161	20,897
Interest expense	(295)	(3,010)	(7,752)	(12,043)
Loss on early extinguishment of debt			(938)	
	2,353	(1,537)	9,471	8,854
Net loss before income tax expense	(32,246)	(13,071)	(80,359)	(105,600)
Income tax expense (benefit)	(728)		2,351	
Net loss	$ (31,518)	$ (13,071)	$ (82,710)	$ (105,600)
Net loss per share amounts, basic and diluted	$ (0.40)	$ (0.19)	$ (1.05)	$ (1.59)
Weighted average shares outstanding, basic and diluted	79,190	67,754	78,827	66,334

Source: Regeneron Pharmaceuticals, Inc.

Regeneron Pharmaceuticals, Inc.
Investor Relations:
Peter Dworkin, 914-345-7640
peter.dworkin@regeneron.com
or
Media Relations:
Laura Lindsay, 914-345-7800
laura.lindsay@regeneron.com
or
Kelly Hershkowitz, 212-845-5624
khershkowitz@biosector2.com

REGENERON

Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion

April 30, 2009

Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein OcclusionTwo Phase 3 studies to start in the second half of this year

BERLIN and TARRYTOWN, N.Y., April 30 /PRNewswire-FirstCall/ -- Bayer HealthCare AG and Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that the companies are extending their global development program for VEGF Trap-Eye, an investigational agent for the treatment of certain eye diseases, to include Central Retinal Vein Occlusion (CRVO). The companies plan to initiate a Phase 3 program evaluating the efficacy and safety of VEGF Trap-Eye in the treatment of CRVO in the second half of this year. CRVO is caused by obstruction of the central retinal vein that that leads to a back up of blood and fluid in the retina, resulting in retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of abnormal new blood vessels that can cause further vision loss and more serious complications.

The Phase 3 program in CRVO will consist of two, multinational, one-year clinical studies which have been reviewed with regulatory authorities. These studies will expand the companies' global development collaboration for VEGF Trap-Eye, which already includes two ongoing Phase 3 studies in patients with the neovascular form of Age-related Macular Degeneration (wet AMD) and a Phase 2 study in patients with Diabetic Macular Edema (DME). Enrollment in the wet AMD and DME studies is expected to be completed later this year.

"Although CRVO is a leading cause of blindness, there is currently no treatment available that can be universally considered to be the standard of care, and there is no approved treatment to prevent the loss of vision or improve vision once it is lost," said Dr. Kemal Malik, Head of Global Development and member of the Bayer HealthCare Executive Committee. "Since the underlying biology of CRVO is related to edema and the growth of abnormal new blood vessels that are mediated by vascular endothelial growth factor (VEGF), we are hopeful that VEGF Trap-Eye may help address this significant unmet medical need."

About CRVO

Over 100,000 people in the United States are estimated to suffer from CRVO. CRVO is caused by obstruction of the central retinal vein that leads to a back up of blood and fluid in the retina, resulting in retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new abnormal blood vessels that can cause further vision loss and more serious complications. Release of VEGF contributes to increased vascular permeability in the eye and abnormal new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the growth of abnormal new blood vessels in the retina in patients with CRVO.

About the Phase 3 CRVO Program

In the Phase 3 CRVO program for VEGF Trap-Eye, Regeneron and Bayer HealthCare will conduct two identical multinational clinical studies: COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) will be led by Regeneron and GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) will be led by Bayer HealthCare. Enrollment will be initiated later in 2009.

Patients in both studies will receive 6 monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 milligrams (mg) or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after 6 months of treatment. At the end of the initial 6 months, all patients will be dosed on a PRN (as needed) basis for another 6 months. All patients will be eligible for rescue laser treatment.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye and vascular permeability and edema. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). Investigational VEGF Trap-Eye is a specific blocker of VEGF-A and PlGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors.

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, DME, CRVO, and other eye diseases and disorders. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc. is the U.S.-based pharmaceuticals operation of Bayer HealthCare, an affiliate of Bayer AG. One of the world's

leading, innovative companies in the healthcare and medical products industry, Bayer HealthCare combines the global activities of the Animal Health, Consumer Care, Diabetes Care, and Pharmaceuticals divisions. In the United States, Bayer HealthCare Pharmaceuticals comprises the following business units: Women's Healthcare, Diagnostic Imaging, General Medicine, Hematology/Neurology, and Oncology. The company's aim is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

Forward-Looking Statements - Bayer HealthCare AG

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Forward Looking Statement -- Regeneron Pharmaceuticals, Inc.

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

SOURCE Regeneron Pharmaceuticals, Inc.; Bayer HealthCare AG

-0- 04/30/2009
/CONTACT: Anna Koch, Bayer HealthCare, +49-30-468-15942, anna.koch@bayerhealthcare.com, or Rose Talarico, +1-973-305-5302, rose.talarico@bayer.com; or Peter Dworkin, Investor Relations, +1-914-345-7640, peter.dworkin@regeneron.com, or Laura Lindsay, Media Relations, +1-914-345-7800, laura.lindsay@regeneron.com, or Olga Fleming, Media Relations, +1-212-845-5636, ofleming@biosector2.com, all of Regeneron Pharmaceuticals, Inc./
/Web Site: http://www.regeneron.com

http://www.bayer.com /
(REGN)

CO: Regeneron Pharmaceuticals, Inc.; Bayer HealthCare AG; Bayer HealthCare Pharmaceuticals Inc.

ST: Germany, New York
IN: HEA MTC
SU: TRI JVN

PR
-- NY08289 --
8289 04/30/2009 02:00 EDT http://www.prnewswire.com

REGENERON

First Patient Enrolled in Regeneron and Bayer HealthCare VEGF Trap-Eye Phase 3 Program in Central Retinal Vein Occlusion

July 23, 2009

First Patient Enrolled in Regeneron and Bayer HealthCare VEGF Trap-Eye Phase 3 Program in Central Retinal Vein OcclusionTARRYTOWN, N.Y.--(BUSINESS WIRE)--Jul. 23, 2009-- Regeneron Pharmaceuticals, Inc. **(NASDAQ:REGN)** today announced that the first patient has been enrolled in the Phase 3 program of VEGF Trap-Eye for the treatment of central retinal vein occlusion (CRVO), a leading cause of blindness in adults. Regeneron received a $20 million milestone payment from Bayer Healthcare that was triggered by the dosing of the first patient in the CRVO program. Regeneron also announced that enrollment in the Phase 2 DA VINCI study of VEGF Trap-Eye in diabetic macular edema (DME) has been completed and data are expected during the first half of 2010.

VEGF Trap-Eye, an investigational drug, is being developed by Regeneron and Bayer HealthCare AG for the potential treatment of eye diseases, including the neovascular form of age-related macular degeneration (wet AMD), DME, and CRVO.

The Phase 3 program in CRVO consists of two multinational, one-year clinical studies. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron and the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. Patients in both studies will receive six monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 milligrams (mg) or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. At the end of the initial six months, patients will be dosed on a PRN (as needed) basis for another six months. All patients will be eligible for rescue laser treatment. Results from both CRVO studies are expected in 2011.

In wet AMD, Regeneron and Bayer Healthcare are evaluating VEGF Trap-Eye in two ongoing Phase 3 studies, known as VIEW 1 and VIEW 2 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration). Enrollment in these trials is expected to be completed by the end of this year, and data are expected in late 2010.

Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States. Bayer HealthCare has exclusive rights to market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye.

About CRVO

Over 100,000 people in the United States are estimated to suffer from CRVO, a disease for which there is no current treatment that can be considered standard of care. CRVO is caused by obstruction of the central retinal vein that leads to a back up of blood and fluid in the retina, resulting in retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new abnormal blood vessels that can cause further vision loss and more serious complications. Release of VEGF contributes to increased vascular permeability in the eye and abnormal new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the growth of abnormal new blood vessels in the retina in patients with CRVO.

About DME

Diabetic Retinopathy (DR) can lead to significant vision impairment and is a major complication of diabetes. Diabetic Macular Edema (DME) is a common complication of DR that involves fluid collection in the macula. DME is the most prevalent cause of moderate visual loss in patients with diabetes.

DME is a leading cause of adult blindness in the developed world. Severe visual loss is caused by a combination of fluid build-up around the retina and the unnatural growth of blood vessels in the back of the eye.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye and vascular permeability and edema. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). Investigational VEGF Trap-Eye is a specific blocker of VEGF-A and PlGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product in the United States, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008 and Form 10-Q for the quarter ended March 31, 2009. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

Source: Regeneron Pharmaceuticals, Inc.

Regeneron Pharmaceuticals, Inc.
Peter Dworkin, 914-345-7640
Investor Relations
peter.dworkin@regeneron.com
or
Laura Lindsay, 914-345-7800
Media Relations
laura.lindsay@regeneron.com

REGENERON

Regeneron Schedules November 22, 2010 Teleconference and Webcast to Discuss Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration

November 19, 2010

TARRYTOWN, N.Y., Nov. 19, 2010 /PRNewswire-FirstCall/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that it will hold a teleconference and webcast at 8:30 a.m. Eastern Time on Monday, November 22, to discuss results of two Phase 3 studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration, VIEW 1 and VIEW 2, and its VEGF Trap-Eye program. A press release will be issued on Monday prior to the call.

Teleconference/Webcast Details

To participate in the live call on Monday, November 22, at 8:30 a.m. Eastern Time, please dial (877) 390-5538 for domestic callers and (408) 940-3843 for international callers, participant code 27197068. The live conference call is being webcast and it can be accessed on the "Newsroom" page of the Company's web site, www.regeneron.com. The webcast will be available for 30 days following the call.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Contact Information:

Michael Aberman, M.D.	Peter Dworkin
Investor Relations	Corporate Communications
914.345.7799	914.345.7640
michael.aberman@regeneron.com	peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

Regeneron and Bayer Start Phase 3 Trial to Extend Ophthalmology Research & Development Program for VEGF Trap-Eye in Asia

January 18, 2011

TARRYTOWN, N.Y., BERLIN and SINGAPORE, Jan. 18, 2011 /PRNewswire/ -- Regeneron (Nasdaq: REGN) and Bayer HealthCare today announced initiation of a new Phase 3 clinical trial in collaboration with the Singapore Eye Research Institute (SERI) investigating the efficacy and safety of VEGF Trap-Eye (aflibercept ophthalmic solution) in patients with choroidal neovascularisation (CNV) of the retina as a result of pathologic myopia. The trial has started in Japan and other Asian countries, including China, Korea, Singapore, and Taiwan.

Myopia is one of the most common eye conditions and is highly prevalent in Asian populations, including Singapore where 40% of adults have myopia and nearly 10% have high myopia. Myopic CNV is a complication of high myopia where abnormal blood vessels grow and leak blood and fluid into the retina as a result of degenerative changes in the retinal lining of the eye and is a potentially blinding condition. Currently, there is no well-established treatment for myopic CNV. VEGF Trap-Eye has previously met its primary efficacy endpoint in a Phase 3 trial for neovascular (wet) age-related macular degeneration (AMD).

Collaboration with the Singapore Eye Research Institute (SERI)

SERI has been appointed as the Asian reading center partner for this study. The Singapore Advanced Imaging Laboratory for Ocular Research (SAILOR) will serve as the first reading center for VEGF Trap-Eye studies in the region. SAILOR brings together an inter-disciplinary group of clinician researchers and scientists to collaborate on cutting-edge computer image research. SAILOR is the first clinical translational research unit to be located in Fusionopolis, a research and development complex in Singapore, and serves as a hub of translational research programs in ocular imaging among clinicians, scientists, computer scientists, and other experts. One of the major programs SAILOR has developed is a "tele-ophthalmic ocular imaging platform" to allow transfer and data capture of ocular images for diagnosis and screening. SAILOR will read the images for this myopic CNV trial from the different Asian sites.

"Myopia is a common problem in Singapore and Asia. In particular, myopic CNV, which affects certain groups of people with higher degrees of myopia, may lead to vision loss. There remains uncertainty regarding the best methods of treatment for myopic CNV and this new trial will go towards addressing this clinical need," said Prof. Wong Tien Yin, Director of SERI and Co-Director of SAILOR.

About mCNV

Myopic choroidal neovascularization is a disease of the retina where new, abnormal blood vessels grow into the retina in persons who are severely myopic (typically more than minus six diopters) and have pathological changes in the back of the eye. In myopic patients, the eyeball is too long, which puts strain on the retina and leads to those pathological changes. Anti-VEGF treatment has been shown to be effective in wet age-related macular degeneration, which is also characterised by the growth of new, abnormal blood vessels in the retina. Severe myopia is particularly common in Asia, with some scientists believing that it may be generally more common in Asians than in people from European descent. Myopic CNV (mCNV) is associated with high degrees of myopia and leads to progressive loss of the patient's sight, ending in blindness. In East Asia, the prevalence of myopia is significantly higher than in the West Asia, and seems to have an earlier onset. In Japan, mCNV is the second most common cause of blindness.

About the mCNV Trial

The Phase 3 myopic CNV trial, named MYRROR, will enroll approximately 250 patients and has started in Japan. Other Asian countries, including Singapore, China, Korea, and Taiwan, will join this clinical study throughout the year. Three out of four patients in the trial will receive an injection of VEGF Trap-Eye into the affected eye (and repeated injections on a PRN, as needed, basis, if required). One out of four patients will receive a sham procedure. The clinical outcome of the two treatment groups after 24 weeks will be assessed by a different team of doctors who are unaware of what treatment the patients received. From week 24 onward, sham patients may receive active treatment. The primary outcome measure of the trial is the mean change in vision (best corrected visual acuity) after 24 weeks, compared to baseline. Secondary outcome measures include the percentage of patients who gain or lose certain amounts of letters in the visual test, changes in retinal thickness from baseline, changes in the total mCNV lesion size, and vessel leakage as seen on an angiogram of the affected eye. The study is scheduled to run until June 2013.

About VEGF Trap-Eye

VEGF Trap-Eye is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Bayer HealthCare and Regeneron are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age-related macular degeneration (wet AMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO), and other eye diseases and disorders.

In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four

treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval for the treatment of wet AMD in Europe and the U.S. in the first half of 2011.

Trials in other indications such as CRVO and DME are currently underway or in preparation.

Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Singapore Eye Research Institute (SERI)

SERI is the national research institute for ophthalmic and vision research in Singapore. Serving as the research institute of the Singapore National Eye Centre, and affiliated to the Yong Loo Lin School of Medicine, National University of Singapore, as well the Duke-NUS Graduate Medical School, SERI undertakes vision research in collaboration with local clinical ophthalmic centers and biomedical research institutions, as well as major eye centers and research institutes throughout the world. For further information, kindly visit www.seri.com.sg.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 15,988 million (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group, Bayer HealthCare, and Astellas to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2009 and Form 10-Q for the quarter ended September 30, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Your Contact at Bayer:
Doreen Schroeder, Tel. +49 30 468-11399
E-Mail: doreen.schroeder@bayer.com

Your Investor Relations Contact at Regeneron:
Michael Aberman, M.D. Tel. +1 (914) 345-7799
E-Mail: michael.aberman@regeneron.com

Your Media Contact at Regeneron:
Peter Dworkin, Tel. +1 (914) 345-7640
E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals

News Provided by Acquire Media

REGENERON

Regeneron to Webcast Investor Briefing on VEGF Trap-Eye Clinical Program on Sunday, February 13th at 9 am ET

February 9, 2011

TARRYTOWN, N.Y., Feb. 9, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that it will webcast an investor briefing on Sunday, February 13 from 9 a.m. to 10:30 a.m. Eastern Time. At the investor briefing, principal investigators from the VEGF Trap-Eye clinical studies will recap presentations from the Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2011 meeting being held in Miami, Florida on Saturday, February 12 .

The investigator presentations will provide additional data from the VIEW 1 and VIEW 2 Phase 3 trials in patients with the neovascular form of age-related macular degeneration (wet AMD), the COPERNICUS Phase 3 trial in macular edema due to central retinal vein occlusion (CRVO), and the DA VINCI Phase 2 trial in diabetic macular edema (DME). Regeneron reported positive top-line results from all these trials in the fourth quarter of 2010.

"It's a privilege to be able to release this important collection of VEGF Trap-Eye data at the Bascom Palmer Eye Institute's Eighth Annual Angiogenesis Meeting," said Philip J. Rosenfeld, M.D., Ph.D., Professor of Ophthalmology, University of Miami Miller School of Medicine and Course Co-Director of the Angiogenesis 2011 Meeting. "In particular, the Phase 3 results in wet AMD suggest that the VEGF Trap-Eye has the potential to address an important unmet need of providing optimal vision gain while reducing the burden of intravitreal injections and office visits for patients and their caregivers."

The webcast and slides may be accessed through the Company's web site, www.regeneron.com, on the Investor Relations page (http://investor.regeneron.com). An archived version of the presentation will be available after the live webcast through March 17, 2011.

About VEGF Trap-Eye

VEGF Trap-Eye is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, DME, CRVO, myopic CNV, and other eye diseases and disorders. The companies plan to submit regulatory applications for marketing approval for VEGF Trap-Eye for the treatment of wet AMD in Europe and the U.S. in the first-half of 2011. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters and were balanced across all treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms.

Trials in other indications such as CRVO and DME are currently underway or in preparation.

About Wet Age-Related Macular Degeneration (wet AMD)

Age-related macular degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating distortion and/or blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe. It is estimated that more than 210,000 Americans are newly diagnosed with and treated for wet AMD each year.

About Central Retinal Vein Occlusion (CRVO)

Over 100,000 people in the United States and more than 66,000 people in key European countries are estimated to suffer from central retinal vein occlusion (CRVO). CRVO is caused by obstruction of the central retinal vein that leads to a back up of blood and fluid in the retina. This causes retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the inappropriate growth of new blood vessels in the retina in patients with CRVO.

About Diabetic Macular Edema (DME)

Diabetic macular edema (DME) is the most prevalent cause of moderate vision loss in patients with diabetes. DME is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME is a leading cause of blindness in younger adults (under 50). Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for

sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

Approximately 370,000 Americans currently suffer from clinically significant DME, with 95,000 new cases arising each year. According to the American Diabetes Association, more than 18 million Americans currently suffer from diabetes, and many other people are at risk for developing diabetes. With the incidence of diabetes steadily climbing, it is projected that up to 10 percent of all patients with diabetes will develop DME during their lifetime.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2009 and Form 10-Q for the quarter ended September 30, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Investor Relations Contact:
Michael Aberman, M.D. Tel. +1 (914) 345-7799
E-Mail: michael.aberman@regeneron.com

Media Contact:
Peter Dworkin, Tel. +1 (914) 345-7640
E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

Back

February 22, 2011 at 8:00 AM EST

REGENERON SUBMITS BIOLOGICS LICENSE APPLICATION TO FDA FOR VEGF TRAP-EYE FOR TREATMENT OF WET AGE-RELATED MACULAR DEGENERATION

TARRYTOWN, N.Y., Feb. 22, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that the company submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for VEGF Trap-Eye for the treatment of the neovascular form of age-related macular degeneration (wet AMD). Under the Prescription Drug User Fee Act (PDUFA), the goal for a standard review time from submission to FDA action is ten months. Regeneron's submission includes a request for Priority Review, which, if granted, would shorten the FDA's targeted goal for review time under PDUFA to six months.

"There have been significant advances in the treatment of wet AMD in recent years. However, the need for monthly intravitreal injections to obtain optimal vision gains has resulted in a significant burden for physicians, patients, and their caregivers," said Leonard S. Schleifer, M.D., Ph.D., President and Chief Executive Officer of Regeneron. "We are extremely proud to have conducted the largest global Phase 3 clinical program in patients with wet AMD, which demonstrated that patients treated with VEGF Trap-Eye 2 mg every two months, following three loading doses, were able to be dosed with fewer injections over one year without compromising efficacy. We look forward to working closely with the FDA to bring this potentially important new medicine to patients with wet AMD."

The VEGF Trap-Eye BLA is based on the positive results from two Phase 3 trials, the North American VIEW 1 trial and the global VIEW 2 trial. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed 2 milligrams (mg) every two months (following three loading doses), successfully met the primary endpoint of non-inferiority, compared to the current standard of care, ranibizumab 0.5 mg dosed every month. The primary endpoint analysis was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The ocular adverse events were balanced across all treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms.

About the VIEW Program

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1024 of 2000

The VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) program consists of two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD). The VIEW 1 study, which randomized 1217 patients, is being conducted in the United States and Canada by Regeneron under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration. The VIEW 2 study, which randomized 1240 patients, is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The study designs are essentially identical. The primary endpoint evaluation was conducted at 52 weeks.

In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5 mg monthly, 2.0 mg monthly, or 2.0 mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5 mg every month during the first year of the studies.

The primary endpoint of these non-inferiority studies was the proportion of patients treated with VEGF Trap-Eye who maintained visual acuity at the end of one year, compared to ranibizumab patients. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity. Maintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart.

The following table summarizes the VIEW 1 and VIEW 2 results for the primary and the first secondary endpoint pre-specified for testing:

	Ranibizumab 0.5mg monthly	**VEGF Trap-Eye 0.5mg monthly**	**VEGF Trap-Eye 2mg monthly**	**VEGF Trap-Eye 2mg every 2 months**
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%**	95.1%**	95.1%**
VIEW 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5mg monthly)***				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

*Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart

**Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)

*** Test for superiority

NS=not statistically significant

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1025 of 2000

In the VIEW 1 and VIEW 2 trials, a generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation, breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

As-needed (PRN) dosing with both agents, with a dose administered at least every three months (but not more often than monthly), is being evaluated during the second year of VIEW 1 and VIEW 2. These studies are part of the global development program for VEGF Trap-Eye being conducted by Regeneron and Bayer HealthCare.

About VEGF Trap-Eye

VEGF Trap-Eye is a fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 that binds all forms of VEGF-A, along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the development of VEGF Trap-Eye for the treatment of wet AMD, central retinal vein occlusion, diabetic macular edema, myopic choroidal neovascularisation, and other eye diseases and disorders. Bayer HealthCare intends to submit regulatory applications in the first half of 2011 for marketing approval in Europe. If approved by regulatory authorities, Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Wet Age-Related Macular Degeneration (wet AMD)

Age-related macular degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating distortion and/or blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe. It is estimated that more than 210,000 Americans are newly diagnosed with and treated for wet AMD each year.

About Central Retinal Vein Occlusion (CRVO)

Over 100,000 people in the United States and more than 66,000 people in key European countries are estimated to suffer from central retinal vein occlusion (CRVO). CRVO is caused by obstruction of the central retinal vein that leads to a back up of blood and fluid in the retina. This causes retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new, inappropriate blood vessels that can cause further vision

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1026 of 2000

loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the inappropriate growth of new blood vessels in the retina in patients with CRVO.

About Diabetic Macular Edema (DME)

Diabetic macular edema (DME) is the most prevalent cause of moderate vision loss in patients with diabetes. DME is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME is a leading cause of blindness in younger adults (under 50). Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

Approximately 370,000 Americans currently suffer from clinically significant DME, with 95,000 new cases arising each year. According to the American Diabetes Association, more than 18 million Americans currently suffer from diabetes, and many other people are at risk for developing diabetes. With the incidence of diabetes steadily climbing, it is projected that up to 10 percent of all patients with diabetes will develop DME during their lifetime.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Investor Relations Contact:

Michael Aberman, M.D. Tel. +1 (914) 345-7799

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1027 of 2000

E-Mail: michael.aberman@regeneron.com

Media Contact:

Peter Dworkin, Tel. +1 (914) 345-7640

E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

Investor Relations
914.847.7741
invest@regeneron.com

Media Relations
media@regeneron.com

Investor email alerts

DOWNLOAD CENTER

- 2020 Proxy Statement
- 2019 Annual Report
- 2019 Responsibility Report
- 2019 Form 10-K
- Senior Management Biographies
- Corporate Fact Sheet
- Regeneron Genetics Center Backgrounder

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1028 of 2000

Investor Relations
914.847.7741
invest@regeneron.com

Media Relations
media@regeneron.com

Investor email alerts



Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1029 of 2000

REGENERON

Regeneron and Bayer Announce Start of Phase 3 Clinical Program in Diabetic Macular Edema

April 8, 2011

Tarrytown, NY, USA, and Berlin, Germany, April 8, 2011 -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Bayer HealthCare today announced that they have initiated the first of two Phase 3 clinical trials evaluating the efficacy and safety of VEGF Trap-Eye (aflibercept ophthalmic solution), an investigational new agent for the treatment of certain eye diseases, in the treatment of Diabetic Macular Edema (DME). The companies are extending their development program for VEGF Trap-Eye in DME after promising results in the global Phase 2 DME program.

The first Phase 3 trial in DME, named VIVID-DME, is being led by Bayer HealthCare and has started in Australia. The trial will also be conducted in Europe and Japan. A second study led by Regeneron, named VISTA-DME, is expected to begin later in 2011 in the United States, Canada, and other countries.

"Clinically significant DME is a leading cause of vision loss in adults under the age of 50 suffering from diabetes," said Dr. Kemal Malik, Head of Global Development and member of the Bayer HealthCare Executive Committee. "After reporting positive results from our global Phase 3 program (VIEW 1 and VIEW 2 studies) for the treatment of the neovascular form of age-related macular degeneration (wet AMD), we are pleased to start a Phase 3 program with VEGF Trap-Eye in DME which may help to address this significant unmet medical need."

The Phase 3 program in DME expands the companies' global development collaboration for VEGF Trap-Eye. The companies announced positive data for two Phase 3 studies in patients with wet AMD in November 2010 and for the first of two Phase 3 studies in patients with Central Retinal Vein Occlusion (CRVO) in December 2010.

About the Phase 3 DME Program
The VIVID-DME study (**V**EGF Trap-Eye **I**n **V**ision Impairment **D**ue to **DME**) has three study arms. In the first arm, patients will be treated every month with 2 milligrams (mg) of VEGF Trap-Eye. In the second arm, patients will be treated with 2mg of VEGF Trap-Eye every two months after a loading phase of monthly injections. In the third arm, the comparator arm, patients will be treated with macular laser photocoagulation. The primary endpoint is mean change in visual acuity from baseline as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity. All patients will be followed for three years. The VISTA-DME study (**V**EGF Trap-Eye: **I**nvestigation of **S**afety, **T**reatment effect, and **A**natomic outcomes in **DME**) is expected to begin later in 2011.

About Diabetic Macular Edema (DME)
DME is the most prevalent cause of moderate vision loss in patients with diabetes. DME is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME is a leading cause of blindness in younger adults (under 50). Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

According to figures from the World Health Organization, DME is the second leading cause of blindness in Western industrialized countries. In Europe, about 8% of the population is affected by diabetes. Approximately 370,000 Americans currently suffer from clinically significant DME, with 95,000 new cases arising each year. According to the American Diabetes Association, over 18 million Americans currently suffer from diabetes, and many more are at risk for developing diabetes. The incidence of diabetes is steadily climbing and it is projected that up to 10 percent of all patients with diabetes will develop DME during their lifetime.

About VEGF Trap-Eye
Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as diabetes, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit vascular permeability and lead to edema. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with another vascular growth factor, the Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of VEGF-A and PlGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors. Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

Regeneron submitted a Biologics License Application for marketing approval in wet age-related macular degeneration (wet AMD) in the US in February 2011, and Bayer plans to submit a regulatory application outside the US in the first half of 2011. Phase 3 studies in central retinal vein occlusion (CRVO) and in patients with choroidal neovascularisation (CNV) of the retina as a result of pathologic myopia - a major eye disease common in Asia - are currently underway.

About Regeneron Pharmaceuticals
Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 16.913 billion (2010), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 55.700 employees (Dec 31, 2010) and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward-Looking Statements

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

To learn more about Age-related macular degeneration (AMD), please visit:
www.bayerpharma.com.

Your Contact at Bayer:
Doreen Schroeder, Tel. +49 30 468-11399
E-Mail: doreen.schroeder@bayer.com

Your Investor Relations Contact at Regeneron:
Michael Aberman, MD., Tel. +1 (914) 345-7799
E-Mail: michael.aberman@regeneron.com

Your Media Contact at Regeneron:
Peter Dworkin, Tel. +1 (914) 345-7640
E-Mail: peter.dworkin@regeneron.com

REGENERON

FDA Grants Priority Review for VEGF Trap-Eye for the Treatment of Wet Age-Related Macular Degeneration

April 18, 2011

TARRYTOWN, N.Y., April 18, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the Company's Biologics License Application (BLA) for VEGF Trap-Eye for the treatment of the neovascular form of age-related macular degeneration (wet AMD). The FDA also granted the Company's request for priority review of its BLA. A Priority Review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. Under priority review, the target date for an FDA decision on the VEGF Trap-Eye BLA is August 20, 2011.

"We are very pleased that the FDA has chosen to grant priority review to VEGF Trap-Eye. We look forward to working closely with the FDA to achieve our goal of bringing a new treatment option that offers a major advance to patients with age-related macular degeneration," said Leonard S. Schleifer, M.D., Ph.D., President and Chief Executive Officer of Regeneron.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as diabetes, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit vascular permeability and lead to edema. VEGF Trap-Eye is a fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. VEGF Trap-Eye binds all forms of VEGF-A, along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the development of VEGF Trap-Eye for the treatment of wet AMD, central retinal vein occlusion, diabetic macular edema, myopic choroidal neovascularisation, and other eye diseases and disorders. Bayer HealthCare intends to submit a regulatory application outside of the United States in the first half of 2011. If approved by regulatory authorities, Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statements

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of our product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of our late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict our ability to continue to develop or commercialize our product and drug candidates, competing drugs that may be superior to our product and drug candidates, uncertainty of market acceptance of our product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including our agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Contact Information:

Michael Aberman, M.D.	Peter Dworkin
Investor Relations	Corporate Communications
914.345.7799	914.345.7640
michael.aberman@regeneron.com	peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

VEGF Trap-Eye Submitted for EU Marketing Authorization for Treatment of Wet Age-Related Macular Degeneration

June 7, 2011

TARRYTOWN, N.Y. and BERLIN, June 7, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) and Bayer HealthCare today announced that Bayer HealthCare has submitted an application for marketing authorization in Europe for VEGF Trap-Eye for the treatment of the neovascular form of age-related macular degeneration (wet AMD). Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of wet AMD, central retinal vein occlusion (CRVO), diabetic macular edema (DME), and myopic choroidal neovascularization (mCNV).

"The submission of VEGF Trap-Eye for EU marketing authorization represents a significant milestone in our goal to bring this potentially important new therapy to patients with wet AMD across the globe," said Leonard S. Schleifer, M.D., Ph.D., President and Chief Executive Officer of Regeneron.

The VEGF Trap-Eye submission is based on the positive results from two Phase 3 trials, the VIEW 1 study and the VIEW 2 study. In these trials, all regimens of VEGF Trap-Eye, including 2 mg VEGF Trap-Eye dosed every two months (following three loading doses), successfully met the primary endpoint of non-inferiority, compared to the current standard of care, ranibizumab 0.5 mg dosed every month. The primary endpoint analysis was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab at the dose that is currently known to provide the best possible efficacy. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The ocular adverse events were balanced across all treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms.

Regeneron submitted a Biologics License Application (BLA) for marketing approval in wet AMD in the U.S. in February 2011 and received a Priority Review designation.

Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally the profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About the VIEW Program

The VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) program consists of two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD). The VIEW 1 study, which randomized 1,217 patients, is being conducted in the United States and Canada by Regeneron under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration. The VIEW 2 study, which randomized 1,240 patients, is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The study designs are essentially identical. The primary endpoint evaluation was conducted at 52 weeks.

In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5 mg monthly, 2 mg monthly, or 2 mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5 mg every month during the first year of the studies. As-needed (PRN) dosing with both agents, with a dose administered at least every three months (but not more often than monthly) is being evaluated during the second year of each study.

About VEGF Trap-Eye

VEGF Trap-Eye is a fully human fusion protein, consisting of portions of VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), central retinal vein occlusion (CRVO), diabetic macular edema (DME), myopic choroidal neovascularization (mCNV), and other eye diseases and disorders.

Regeneron submitted a Biologics License Application (BLA) for marketing approval in wet AMD in the U.S. in February 2011 and received a Priority Review designation. Under Priority Review, the target date for an FDA decision on the VEGF Trap-Eye BLA is August 20, 2011.

In April 2011, Bayer HealthCare and Regeneron announced the initiation of a Phase 3 program in DME.

Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally the profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration, central retinal vein occlusion, and diabetic macular edema), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 16.913 billion (2010), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 55.700 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward-Looking Statements

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that may be superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010 and Form 10-Q for the quarter ended March 31, 2011 . Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Your Contact at Bayer:
Doreen Schroeder, Tel. +49 30 468-11399
E-Mail: doreen.schroeder@bayer.com

Your Investor Relations Contact at Regeneron:
Michael Aberman, M.D., Tel. +1 (914) 345-7799
E-Mail: michael.aberman@regeneron.com

Your Media Contact at Regeneron:
Peter Dworkin, Tel. +1 (914) 345-7640
E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

Regeneron Announces EYLEA™ (aflibercept ophthalmic solution) Receives Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee

June 17, 2011

TARRYTOWN, N.Y., June 17, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) today announced that the Dermatologic and Ophthalmic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) has voted unanimously to recommend that the FDA approve EYLEA™, also known as VEGF Trap-Eye, for the treatment of the neovascular form of age-related macular degeneration (wet AMD) at a dose of 2 milligrams (mg) every eight weeks, following three initial doses given every four weeks.

The committee's recommendation will be considered by the FDA in its review of the Biologics License Application (BLA) for EYLEA, but the committee's recommendation is not binding on the FDA. Regeneron submitted a BLA for marketing approval in wet AMD in the U.S. in February 2011 and received a Priority Review designation. Under Priority Review, the target date for an FDA decision on the EYLEA BLA is August 20, 2011.

"The positive recommendation by the advisory committee is an important step toward providing wet AMD patients with a new treatment option that could potentially reduce the burden that exists with current therapies," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "We look forward to continuing to work with the FDA as it completes its evaluation of the EYLEA BLA."

About EYLEA

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as age-related macular degeneration, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit vascular permeability and lead to edema.

EYLEA (aflibercept ophthalmic solution), also known as VEGF Trap-Eye, is a fully human fusion protein, consisting of portions of VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). EYLEA is a specific and highly potent blocker of these growth factors. EYLEA is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the global development of EYLEA for the treatment of the neovascular form of age-related macular degeneration (wet AMD), central retinal vein occlusion (CRVO), diabetic macular edema (DME), and other eye diseases and disorders. Bayer submitted an application for marketing authorization in Europe in wet AMD in June 2011.

The EYLEA wet AMD regulatory submissions are based on the positive results from two Phase 3 trials, the VIEW 1 study and the VIEW 2 study. In these trials, all regimens of EYLEA, including 2 milligrams (mg) of EYLEA dosed every two months (following three loading doses), successfully met the primary endpoint of non-inferiority compared to the current standard of care, ranibizumab 0.5 mg dosed every month. The primary endpoint analysis was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both EYLEA and ranibizumab. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters.

Bayer HealthCare will market EYLEA™ outside the United States, where the companies will share equally the profits from any future sales of EYLEA. Regeneron maintains exclusive rights to EYLEA in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration, central retinal vein occlusion, and diabetic macular edema), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that may be superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010 and Form 10-Q for the quarter ended March 31, 2011. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Contact Information:

Michael Aberman, M.D.	Peter Dworkin
Investor Relations	Corporate Communications
914.345.7799	914.345.7640
michael.aberman@regeneron.com	peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

August 17, 2011

Regeneron Announces Clinical Presentations at ASRS 2011 Annual Meeting

TARRYTOWN, N.Y., Aug. 17, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that clinical data from four separate clinical studies of EYLEA™ (aflibercept injection) will be presented at the upcoming American Society of Retina Specialists (ASRS) meeting on Sunday, August 21 and Monday, August 22, 2011 in Boston, Massachusetts.

The presentations are:

- "Analysis of 2,457 Patients in the Phase 3 VIEW 1 and VIEW 2 Studies Comparing VEGF Trap-Eye and Ranibizumab in Neovascular AMD" will be presented by Jeffrey S. Heier, M.D. on Sunday, August 21 at 8:21 a.m.

- "One-year Results of the DA VINCI Study of VEGF Trap-Eye in DME" will be presented by Diana V. Do, M.D. on Sunday, August 21 at 2:48 p.m.

- "The 6-Month (Primary Endpoint) Results of the Phase 3 GALILEO Study: VEGF Trap-Eye in CRVO" will be presented by Jean-Francois Korobelnik, M.D. on Monday, August 22 at 8:20 a.m.

- "Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" will be presented by W. Lloyd Clark, M.D. on Monday, August 22 at 8:28 a.m.

About EYLEA™ (aflibercept injection)

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as age-related macular degeneration, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit vascular permeability and lead to edema.

EYLEA, also known as VEGF Trap-Eye, is a fully human fusion protein, consisting of portions of VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). EYLEA is a specific and highly potent blocker of these growth factors. EYLEA is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the global development of EYLEA for the treatment of neovascular age-related macular degeneration (wet AMD), central retinal vein occlusion (CRVO), diabetic macular edema (DME), and other eye diseases and disorders. Bayer submitted an application for marketing authorization in Europe in wet AMD in June 2011.

Bayer HealthCare will market EYLEA™ (aflibercept injection) outside the United States, where the companies will share equally the profits from any future sales of EYLEA. Regeneron maintains exclusive rights to EYLEA in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration, central retinal vein occlusion, and diabetic macular edema), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Contact Information:

Michael Aberman, M.D.
Investor Relations
914.345.7799
michael.aberman@regeneron.com

Peter Dworkin
Corporate Communications
914.345.7640
peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

REGENERON

Regeneron Announces FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration: CORRECTED

November 18, 2011

In the news release, Regeneron Announces FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, issued 18-Nov-2011 by Regeneron Pharmaceuticals, Inc. over PR Newswire, the third paragraph, second sentence, should read "EYLEA offers the potential of achieving the efficacy we've come to expect from current anti-VEGF agents, but with less frequent injections and monitoring." The complete, corrected release follows:

TARRYTOWN, N.Y., Nov. 18, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) today announced that the U.S. Food and Drug Administration (FDA) has approved EYLEA (aflibercept) Injection, known in the scientific literature as VEGF Trap-Eye, for the treatment of patients with neovascular (wet) Age-related Macular Degeneration (AMD) at a recommended dose of 2 milligrams (mg) every four weeks (monthly) for the first 12 weeks, followed by 2 mg every eight weeks (2 months).

The approval of EYLEA was granted under a Priority Review, a designation that is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. This approval was based upon the results of two Phase 3 clinical studies. In these studies, EYLEA dosed every eight weeks, following three initial monthly injections, was clinically equivalent to the standard of care, Lucentis® (ranibizumab injection) dosed every four weeks, as measured by the primary endpoint of maintenance of visual acuity (less than 15 letters of vision loss on an eye chart) over 52 weeks. The most common adverse reactions (frequency of 5% or more) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. The adverse event profile was similar to that seen with ranibizumab.

"The approval of EYLEA offers a much needed new treatment option for patients with wet AMD," said Jeffrey Heier, M.D., a clinical ophthalmologist and retinal specialist at Ophthalmic Consultants of Boston, Assistant Professor of Ophthalmology at Tufts School of Medicine, and Chair of the Steering Committee for the VIEW 1 trial. "EYLEA offers the potential of achieving the efficacy we've come to expect from current anti-VEGF agents, but with less frequent injections and monitoring. This may reduce the need for costly and time-consuming monthly office visits for patients and their caregivers."

"This approval is an important step forward for Regeneron and for patients suffering with wet AMD, the most common cause of blindness in the U.S. in older adults," said Leonard S. Schleifer, M.D., Ph.D., President and Chief Executive Officer of Regeneron. "We thank the patients and clinical investigators who participated in our clinical studies, the FDA, and the Regeneron employees who helped make this day possible. Now that EYLEA is approved, we plan to make EYLEA available to patients within the next few days."

About EYLEA™ (aflibercept) Injection

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as wet age-related macular degeneration, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit abnormal increased permeability that leads to edema. Scarring and loss of fine-resolution central vision often results.

EYLEA, known in the scientific literature as VEGF Trap-Eye, is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) and thereby can inhibit the binding and activation of these cognate VEGF receptors.

EYLEA is indicated for the treatment of patients with neovascular age-related macular degeneration (wet AMD). EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

The recommended dose for EYLEA is 2 mg administered by intravitreal injection every four weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every eight weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every four weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every four weeks compared to every eight weeks.

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was low (1.8%).

Serious adverse reactions related to the injection procedure have occurred in less than 0.1% of intravitreal injections with EYLEA and include endophthalmitis, traumatic cataract, and increased intraocular pressure.

About the VIEW 1 and VIEW 2 Clinical Studies

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW 1 and VIEW 2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to one of four dosing regimens: 1) EYLEA administered 2 mg every eight weeks following three initial

monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every four weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every four weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every four weeks (ranibizumab 0.5Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both the EYLEA™ (aflibercept) Injection 2Q8 and 2Q4 dosing groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5Q4 group for the primary endpoint.

Select results of the VIEW 1 and VIEW 2 studies as described in the full Prescribing Information for the EYLEA 2 mg every four weeks and EYLEA 2 mg every eight weeks dosing groups as compared to ranibizumab dosed monthly group are shown below.

Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW 1 and VIEW 2 Studies

	VIEW 1			**VIEW 2**		
	EYLEA 2 mg Q8 weeks(a)	EYLEA 2 mg Q4 weeks	ranibizu-mab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks(a)	EYLEA 2 mg Q4 weeks	ranibizu-mab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (						

REGENERON

Regeneron and Bayer Initiate Phase 3 Clinical Program for the Treatment of Wet Age-Related Macular Degeneration in China

November 28, 2011

TARRYTOWN, N.Y. and BERLIN, Nov. 28, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) and Bayer HealthCare today announced that they have initiated a Phase 3 clinical trial evaluating the efficacy and safety of EYLEA™ (aflibercept) Injection in the neovascular form of age-related macular degeneration (wet AMD) in China.

The new trial, named SIGHT, will include approximately 300 patients and will be the largest retinal trial conducted in China. SIGHT is being led by Bayer.

"Currently, only photodynamic therapy with verteporfin is approved as a treatment for wet AMD in China, and it is only approved for the subpopulation of patients with predominantly classic wet AMD," said Kemal Malik, M.D., Head of Global Development and member of the Bayer HealthCare Executive Committee. "After reporting positive data from our large VIEW program in wet AMD, we look forward to potentially bringing this new treatment to patients with wet AMD in China."

About the SIGHT Program

The SIGHT (VEGF Trap-Eye: Investigation of Efficacy and Safety in Chinese patients with wet AMD) program consists of a randomized, double-masked, Phase 3 clinical trial evaluating EYLEA (known in the scientific literature as VEGF Trap-Eye) in the treatment of the neovascular form of age-related macular degeneration (wet AMD). EYLEA will be evaluated for its effect on improving and maintaining vision when dosed as an intravitreal injection on a schedule of 2 milligrams (mg) every two months (following three initial monthly doses), as compared with Photodynamic Therapy (PDT) with verteporfin. After assessment of the primary endpoint at week 28, all patients, including those on PDT, will receive EYLEA treatment until the end of the study at week 52. The SIGHT study plans to randomize 300 patients.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe. In China, there were an estimated 540,000 newly diagnosed wet AMD patients over the age of 50 in 2010.

About EYLEA™ (aflibercept) Injection For Intravitreal Injection

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as wet age-related macular degeneration, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit abnormal increased permeability that leads to edema. Scarring and loss of fine-resolution central vision often results.

EYLEA, known in the scientific literature as VEGF Trap-Eye, is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) and thereby can inhibit the binding and activation of these cognate VEGF receptors.

IMPORTANT PRESCRIBING INFORMATION

In this U.S. EYLEA is indicated for the treatment of patients with neovascular age-related macular degeneration (wet AMD).

The recommended dose for EYLEA is 2 mg administered by intravitreal injection every four weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every eight weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every four weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every four weeks compared to every eight weeks.

IMPORTANT SAFETY INFORMATION

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal

stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was low (1.8%).

Serious adverse reactions related to the injection procedure have occurred in less than 0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure.

The most common adverse reactions (greater than or equal to 5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Please see the full Prescribing Information for EYLEA, available online at www.regeneron.com/EYLEA-fpi.pdf.

About the EYLEA™ (aflibercept) Injection Global Collaboration

Regeneron is collaborating with Bayer HealthCare on the global development of EYLEA. Bayer submitted an application for marketing authorization in Europe for wet AMD in June 2011.

Bayer HealthCare will market EYLEA outside the United States, where the companies will share equally the profits from any future sales of EYLEA. Regeneron maintains exclusive rights to EYLEA in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets two products, ARCALYST® (rilonacept) Injection For Subcutaneous Use and EYLEA™ (aflibercept) Injection. Regeneron also has completed several Phase 3 studies and is conducting an additional Phase 3 clinical trial for the product candidate ZALTRAP® (aflibercept) Concentrate for Intravenous Infusion. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on the Regeneron web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 16.913 billion (2010), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 55,700 employees (Dec 31, 2010) and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

To learn more about wet Age-related Macular Degeneration (AMD), please visit www.bayerpharma.com/en/AMD

Regeneron Forward-Looking Statement

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of EYLEA and Regeneron's product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize EYLEA and other products and drug candidates, competing drugs that may be superior to EYLEA and Regeneron's products and drug candidates, uncertainty of market acceptance of EYLEA and Regeneron's products and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010 and Form 10-Q for the quarter ended September 30, 2011. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statement

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Your Contact at Bayer:
Doreen Schroeder, Tel. +49 30 468-11399
E-Mail: doreen.schroeder@bayer.com

Your Investor Relations Contact at Regeneron:
Michael Aberman, MD., Tel. +1 (914) 847-7799
E-Mail: michael.aberman@regeneron.com

Your Media Contact at Regeneron:
Peter Dworkin, Tel. +1 (914) 847-7640
E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1044 of 2000

REGENERON

Two Year Results of Phase 3 Studies with EYLEA™ (aflibercept) Injection in wet AMD Show Sustained Improvement in Visual Acuity

December 5, 2011

Patients in the EYLEA 2mg every eight week group achieved visual acuity gains similar to ranibizumab with 5 fewer injections, on average, over two years
Patients who required the most intense therapy received, on average, 1.4 fewer injections in the EYLEA 2mg every eight week group compared to ranibizumab in the second year

TARRYTOWN, N.Y. and BERLIN, Dec. 5, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) and Bayer HealthCare today announced that in an integrated analysis of two parallel Phase 3 studies (VIEW 1 and VIEW 2) in patients with the neovascular form of age-related macular degeneration (wet AMD), patients treated with EYLEA™ (aflibercept) Injection For Intravitreal Injection showed a sustained improvement in visual acuity at 96 weeks versus baseline. The 52-week results (primary analyses) from these studies have previously been reported.

During the first year of the VIEW 1 and VIEW 2 studies, patients were treated with three different dosing regimens of EYLEA, 0.5 milligram (mg) every four weeks, 2mg every four weeks, and 2mg every eight weeks (following three initial monthly injections), compared to ranibizumab 0.5mg every four weeks. The EYLEA 2mg every eight week regimen was recently approved by the U.S. Food and Drug Administration (FDA), based on efficacy (maintenance of vision) that was clinically equivalent at one year to the monthly ranibizumab regimen. In the second year of the studies, patients were treated with the same dose per injection as in the first year and were evaluated monthly to determine need for retreatment. Patients were treated at least every 12 weeks. All year two analyses were considered exploratory.

In an integrated analysis of the VIEW 1 and VIEW 2 studies, the visual acuity gain from baseline in the EYLEA 2mg every eight week group at week 96 was 7.6 letters compared to 8.4 letters at week 52, with an average of 11.2 injections over two years and 4.2 injections during the second year. The visual acuity gain from baseline in the monthly ranibizumab group at week 96 was 7.9 letters compared to 8.7 letters at week 52, with an average of 16.5 injections over two years and 4.7 injections during the second year. The results of each of the VIEW 1 and VIEW 2 studies were consistent with the integrated analysis.

The overall fewer average number of injections in the second year in the EYLEA 2mg every eight week group compared to the ranibizumab group (4.2 versus 4.7) was driven by the fact that fewer patients needed more intense therapy in the EYLEA group and those patients required fewer injections.

The proportion of patients who required frequent injections (six or more) during the second year was lower in the EYLEA 2mg every eight week group compared to the ranibizumab group (15.9% versus 26.5%). In the 25% of patients who required the most intense therapy (the greatest number of injections), patients in the EYLEA 2mg every eight week group required an average of 1.4 fewer injections in the second year compared to the ranibizumab group (6.6 versus 8.0). In the 25% of patients in each group who had the fewest number of injections in the second year, the average number of injections was similar (approximately 3 for both groups, corresponding to the protocol-mandated minimum number of injections).

A generally favorable safety profile was observed for both EYLEA and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease and/or the aging process. The most frequent ocular adverse events (greater than 10% of patients for the overall study population) were conjunctival hemorrhage, eye pain, retinal hemorrhage, and visual acuity reduced. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events (greater than 1% of patients for the overall study population) were falls, pneumonia, myocardial infarction and atrial fibrillation. There were no notable differences among the study arms. The incidence of arterial thrombotic events as defined by the "Anti-Platelet Trialists" group criteria was 3.2% of patients for ranibizumab and 3.3% of patients in the combined EYLEA groups.

"These second year results confirm the sustainability of the vision gains achieved by EYLEA with a less than monthly dosing frequency. Importantly, the second year data demonstrated that for patients that needed more anti-VEGF treatment, this was achieved with fewer injections using EYLEA," said George D. Yancopoulos, M.D., Ph.D., Chief Scientific Officer of Regeneron and President of Regeneron Laboratories. "As a reminder, the recommended dose for EYLEA is 2mg every eight weeks following three initial monthly injections, which demonstrated visual acuity gains that were clinically equivalent to monthly ranibizumab. Retinal physicians and their wet AMD patients consider the predictable every eight week dosing regimen for EYLEA as a significant advance that helps overcome the challenges of monthly office visits."

Further results from year two of the studies will be presented at upcoming medical conferences.

About the VIEW Program

The VIEW (VEGF Trap: Investigation of Efficacy and Safety in Wet AMD) program consists of two randomized, double-masked, Phase 3 clinical trials evaluating EYLEA in the treatment of the neovascular form of age-related macular degeneration (wet AMD). The VIEW 1 study, which randomized 1217 patients, was conducted in the United States and Canada by Regeneron. The VIEW 2 study, which randomized 1240 patients, was conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The study designs are essentially identical. The primary endpoint evaluation was conducted at 52 weeks.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction

of the retina creating distortion and/or blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About EYLEA™ (aflibercept) Injection For Intravitreal Injection

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. Its normal role in a healthy organism is to trigger formation of new blood vessels (angiogenesis) supporting the growth of the body's tissues and organs. However, in certain diseases, such as wet age-related macular degeneration, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit abnormal increased permeability that leads to edema. Scarring and loss of fine-resolution central vision often results.

EYLEA™ (aflibercept) Injection, known in the scientific literature as VEGF Trap-Eye, is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) and thereby can inhibit the binding and activation of these cognate VEGF receptors.

IMPORTANT PRESCRIBING INFORMATION

In the United States, EYLEA is indicated for the treatment of patients with neovascular age-related macular degeneration (wet AMD).

The recommended dose for EYLEA is 2 mg administered by intravitreal injection every four weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every eight weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every four weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every four weeks compared to every eight weeks.

IMPORTANT SAFETY INFORMATION

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was low (1.8%).

Serious adverse reactions related to the injection procedure have occurred in less than 0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure.

The most common adverse reactions (greater than or equal to 5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Please see the full Prescribing Information for EYLEA, available online at www.regeneron.com/EYLEA.pi.pdf.

About the EYLEA™ (aflibercept) Injection Global Collaboration

Regeneron is collaborating with Bayer HealthCare on the global development of EYLEA. Bayer submitted an application for marketing authorization in Europe for wet AMD in June 2011.

Bayer HealthCare will market EYLEA outside the United States, where the companies will share equally the profits from any future sales of EYLEA. Regeneron maintains exclusive rights to EYLEA in the United States.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets two products, ARCALYST® (rilonacept) Injection For Subcutaneous Use and EYLEA™ (aflibercept) Injection. Regeneron also has completed several Phase 3 studies and is conducting an additional Phase 3 clinical trial for the product candidate ZALTRAP® (aflibercept) Concentrate for Intravenous Infusion. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on the Regeneron web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 16.913 billion (2010), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 55.700 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward-Looking Statement

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of EYLEA and Regeneron's product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize EYLEA and other products and drug candidates, competing drugs that may be superior to EYLEA and Regeneron's products and drug candidates, uncertainty of market acceptance of EYLEA and Regeneron's products and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010 and Form 10-Q for the quarter ended September 30, 2011. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Your Contact at Bayer:
Doreen Schroeder, Tel. +49 30 468-11399
E-Mail: doreen.schroeder@bayer.com

Your Investor Relations Contact at Regeneron:
Michael Aberman, M.D. Tel. +1 (914) 847-7799
E-Mail: michael.aberman@regeneron.com

Your Media Contact at Regeneron:
Peter Dworkin, Tel. +1 (914) 847-7640
E-Mail: peter.dworkin@regeneron.com

SOURCE Regeneron Pharmaceuticals, Inc.

News Provided by Acquire Media

Electronic Patent Application Fee Transmittal				
Application Number:	16159282			
Filing Date:	12-Oct-2018			
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS			
First Named Inventor/Applicant Name:	George D. Yancopoulos			
Filer:	Karl Bozicevic/Kimberly Zuehlke			
Attorney Docket Number:	REGN-008CIPCON4			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1300	1300
		Total in USD ($)		**1300**

Electronic Acknowledgement Receipt	
EFS ID:	39875398
Application Number:	16159282
International Application Number:	
Confirmation Number:	8618
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-008CIPCON4
Receipt Date:	30-JUN-2020
Filing Date:	12-OCT-2018
Time Stamp:	17:44:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1300
RAM confirmation Number	E20206TH44495830
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	0725US05_2020-06-30_RCE_Transmittal.pdf	1352000 fbe72c4d1a7162a2001ef7e2acffdbcdcded8709	no	3
Warnings:					
Information:					
2		0725US05_2020-06-30_Pre_Amend.pdf	38519 590e8dc52c4bfe45e18b7ff08f2bab9ac8bf3398	yes	5

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	5

Warnings:					
Information:					
3	Transmittal Letter	0725US05_2020-06-30_Supp_IDS_trans_REGN-008CIPCON4.pdf	50766 7cc95ccb01a190f408ac5f92e2ddbbb31794d95e	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	0725US05__2020-06-30_Supp_IDS_SB08A_REGN-008CIPCON4.pdf	36089 5d83e275b04c9ec6f11044b9f482ac6739f27d5f	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					

5	Non Patent Literature	BayerNews_20080928_0448_en.pdf	127802 6d6478579d4b400aca428b8b3a577d4030031a53	no	5
Warnings:					
Information:					
6	Non Patent Literature	REGN_Press_Release_Mar_27_2007.pdf	1360202 986d7edd7cdd3899ced99c0603f9540b36f32357	no	2
Warnings:					
Information:					
7	Non Patent Literature	REGN_Press_Release_May_9_2007.pdf	1348579 4aea4c46411524118a56a126ad8880d5628dc9d1	no	2
Warnings:					
Information:					
8	Non Patent Literature	REGN_Press_Release_Aug_1_2007.pdf	2839120 9d80051b30879bcf5163b4639fd18a64ca6b2bb6	no	5
Warnings:					
Information:					
9	Non Patent Literature	REGN_Press_Release_Aug_2_2007.pdf	106077 a6c28091d1985f689be1eccf605d9cbff04cb0eb	no	2
Warnings:					
Information:					
10	Non Patent Literature	REGN_Press_Release_Oct_1_2007.pdf	1457215 f6338613f2aabca358d8b8103489fbbf67826e36	no	3
Warnings:					
Information:					
11	Non Patent Literature	REGN_Press_Release_Feb_27_2008.pdf	3789068 585e6714db309793c0e0f1d5dd74666c3615a379	no	6
Warnings:					
Information:					

12	Non Patent Literature	REGN_Press_Release_Apr_28_2008.pdf	24012 21d51e0e9eb9e2b27059dd2eaf647e2220ef6395	no	2
Warnings:					
Information:					
13	Non Patent Literature	REGN_Press_Release_Aug_19_2008.pdf	23293 5d13932b21799c081aff58b6fa4fc0a8e6b4b825	no	2
Warnings:					
Information:					
14	Non Patent Literature	REGN_Press_Release_Feb_26_2009.pdf	3449787 c5f9143255909 8f3ad1fb2789fde8c0fd873e91e	no	5
Warnings:					
Information:					
15	Non Patent Literature	REGN_Press_Release_Apr_30_2009.pdf	107443 9b7019f9ac83ae628b74e4cf5d36232c548ea7e9	no	2
Warnings:					
Information:					
16	Non Patent Literature	REGN_Press_Release_Jul_23_2009.pdf	1070186 5d38c7318355bbb4bd99263a4d5c178ce9c0eb36	no	2
Warnings:					
Information:					
17	Non Patent Literature	REGN_Press_Release_Nov_19_2010.pdf	350695 b241755a11b1083bf843f27bbf27849ece1d60a6	no	1
Warnings:					
Information:					
18	Non Patent Literature	REGN_Press_Release_Jan_18_2011.pdf	1765835 834d1807fb38ebe24b62e6859d6c78251db8b218	no	3
Warnings:					
Information:					

19	Non Patent Literature	REGN_Press_Release_Feb_9_2011.pdf	1371797 aab4ca6426678222de6ccf81389495a08d533ce5	no	2
Warnings:					
Information:					
20	Non Patent Literature	REGN_Press_Release_Feb_22_2011.pdf	110830 1c15ab6a0cda244ad867d79f5839abc72518963	no	6
Warnings:					
Information:					
21	Non Patent Literature	REGN_Press_Release_Apr_8_2011.pdf	1480611 a13f642ce8b29401bd55e0d61db1de29d171f413	no	2
Warnings:					
Information:					
22	Non Patent Literature	REGN_Press_Release_Apr_18_2011.pdf	17501 a824d1d3a227ce42763b0da65601593f396c765b	no	2
Warnings:					
Information:					
23	Non Patent Literature	REGN_Press_Release_Jun_7_2011.pdf	1463628 41e6c89cfa55d29dff0736ab0e82cebfbec32dea	no	2
Warnings:					
Information:					
24	Non Patent Literature	REGN_Press_Release_Jun_17_2011.pdf	19498 afef5a7b39b651100449db5b31c908297f673434	no	2
Warnings:					
Information:					
25	Non Patent Literature	REGN_Press_Release_Aug_17_2011.pdf	581399 8e96e29aa8c022ae65c25ab110c11f914459e27	no	2
Warnings:					
Information:					

26	Non Patent Literature	REGN_Press_Release_Nov_18_2011.pdf	19527 8864153c02303fe0f6969e05c4cf59b745826f9f3	no	2
Warnings:					
Information:					
27	Non Patent Literature	REGN_Press_Release_Nov_28_2011.pdf	27840 42379aa75f28abacc9ffca7fea7a138a3fcd374f	no	3
Warnings:					
Information:					
28	Non Patent Literature	REGN_Press_Release_Dec_5_2011.pdf	32377 cc45cb0792fb752a70ed96149f7f07e1638ad13f	no	3
Warnings:					
Information:					
29	Fee Worksheet (SB06)	fee-info.pdf	30829 1b6543069ce24d87dc4f008d806b9820ce874237	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	24452525		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,282	10/12/2018	George D. Yancopoulos	REGN-008CIPCON4	8618

96387 7590 07/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
07/01/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

PTOL-90A (Rev. 04/07)

CORRECTED ***Notice of Allowability***	**Application No.** 16/159,282	**Applicant(s)** Yancopoulos, George D.	
	Examiner JON M LOCKARD	**Art Unit** 1647	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to IDS filed 31 March 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 32-42 (renumbered as claims 1-11, respectively) . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1057 of 2000

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 31 March 2020 was filed after the mailing date of the Non-Final rejection on 01 October 2019. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

EXAMINER'S COMMENT

3. The information disclosure statement (IDS) filed 31 March 2020 has been considered by the Examiner. After careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
June 24, 2020

Receipt date: 03/31/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	7070959	2006-07-04	Papadopoulos	
	2	8092803	2012-01-10	Furfine et al.	
	3	10406226	2019-09-10	Dix et al.	
	4	10464992	2019-11-05	Furfine et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0388539	2019-12-26	Dix et al.	
	2	2020/0017572	2020-01-16	Furfine et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1					
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	ANONYMOUS "Anti-VEGF 2019: The State of the Art" Review of Ophthalmology (published August 5, 2019)	
	2	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	
	3	CHUNG et al. "Ziv-aflibercept: A novel angiogenesis inhibitor for the treatment of metastatic colorectal cancer" Am J Heath-Syst Pharm (November 1, 2013) 70:1887-1896	
	4	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	
	5	CROLL et al., "VEGF-mediated inflammation precedes angiogenesis in adult brain" Experimental Neurology (2004) 187:388-402	
	6	DeVRIESE et al., "Antibodies against Vascular Endothelial Growth Factor Improve Early Renal Dysfunction in Experimental Diabetes" J. Am. Soc. Nephrol (2001) 12:993-1000	
	7	EREMINA et al., "Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases" Journal of Clinical Investigation (March 2003) 111(5):707-716	
	8	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	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

Receipt date: 03/31/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159.282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon M. Lockard
Sheet	2	of	2	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	FERRARA, N. "Vascular Endothelial Growth Factor: Molecular and Biological Aspects" Advances in Organ Biology (1999) pp. 1-30	
	10	FERRARA et al., "Clinical applications of angiogenic growth factors and their inhibitors" Nature Medicine (December 1999) 5(12):1359-1364	
	11	FLYVBJERG et al., "Amelioration of Long-Term Renal Changes in Obese Type 2 Diabetic Mice by a Neutralizing Vascular Endothelial Growth Factor Antibody" Diabetes (October 2002) 51:3090-3094	
	12	HOLASH et al., "Vessel Cooption, Regression, and Growth in Tumors Mediated by Angiopoietins and VEGF" Science (June 18, 1999) 284(5422):1994-1998	
	13	KOROBELNIK et al., "Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion" American Academy of Ophthalmology (2014) 121(1):202-208	
	14	MITCHELL, Edith P. "Targeted Therapy for Metastatic Colorectal Cancer: Role of Aflibercept" Clinical Colorectal Cancer (2013) 12(2):73-85	
	15	NOGUERA-TROISE et al., "Blockade of D114 inhibits tumour growth by promoting non-productive angiogenesis" Nature (December 2006) 444:1032-1037	
	16	RUDGE et al., "VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade" PNAS (November 20, 2007) 104(47):18363-18370	
	17	SCHMIDT-ERFURTH et al., "Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration" Ophthalmology (2014) 121:193-201	
	18	SEMERARO et al., "Aflibercept in wet AMD: specific role and optimal use" Drug Design, Development and Therapy (August 2, 2013) 7:711-722	
	19	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	
	20	THURSTON, Gavin "Complementary actions of VEGF and Angiopoietin-1 on blood vessel growth and leakage" J. Anat. (2002) 200:575-580	
	21	XIA et al., "Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis" Blood (July 1, 2003) 102(1):161-168	

Examiner Signature	/JON M LOCKARD/	Date Considered	06/24/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	1	of	5	Attorney Docket Number	REGN-008CIPCON4

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1				

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2019/0290725	2019-09-26	Vitti et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 2004/106378 A2	2004-12-09	Regeneron Pharmaceuticals, Inc.		
	2	WO 2005/000895 A2	2005-01-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	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)	
	2	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)	
	3	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 (April 2009)	
	4	HALLER et al., "VEGF Trap-Eye In CRVO: Primary Endpoint Results of the Phase 3 COPERNICUS Study" ARVO Annual Meeting Abstract (April 2011)	
	5	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 (April 2009)	
	6	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 (June 2011)	
	7	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 (September 2011)	
	8	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 June 8, 2011 on ClinicalTrials.gov (NCT00320775_2006-2011)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	2	of	5	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	9	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 March 16, 2015 on ClinicalTrials.gov (NCT00320775_2015)	
	10	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 December 1, 2011 on ClinicalTrials.gov (NCT00320788_2006-2011)	
	11	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 January 27, 2012 on ClinicalTrials.gov (NCT00320788_2012)	
	12	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 June 8, 2011 on ClinicalTrials.gov (NCT00320814_2006-2011)	
	13	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 December 1, 2011 on ClinicalTrials.gov (NCT00509795_2007-2011)	
	14	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 December 20, 2012 on ClinicalTrials.gov (NCT00509795_2012)	
	15	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 November 1, 2011 on ClinicalTrials.gov (NCT00527423_2007-2011)	
	16	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 June 10, 2013 on ClinicalTrials.gov (NCT00527423_2012-2013)	
	17	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 December 16, 2011 on ClinicalTrials.gov (NCT00637377_2008-2011)	
	18	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 November 28, 2014 on ClinicalTrials.gov (NCT00637377_2012-2014)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	3	of	5	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	19	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)	
	20	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 August 28, 2014 on ClinicalTrials.gov (NCT00789477_2013-2014)	
	21	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)	
	22	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 April 16, 2013 on ClinicalTrials.gov (NCT00943072_2012-2013)	
	23	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 (April 2010)	
	24	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 (April 2011)	
	25	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)	
	26	Regeneron SEC Form 10-K (February 27, 2008)	
	27	Regeneron SEC Form 10-K (February 26, 2009)	
	28	Regeneron SEC Form 10-K (February 17, 2011)	
	29	Regeneron SEC Form 10-Q (May 8, 2006)	
	30	Regeneron SEC Form 10-Q (August 8, 2006)	
	31	Regeneron SEC Form 10-Q (November 6, 2006)	
	32	Regeneron SEC Form 10-Q (May 4, 2007)	
	33	Regeneron SEC Form 10-Q (August 3, 2007)	
	34	Regeneron SEC Form 10-Q (April 30, 2009)	
	35	Regeneron SEC Form 10-Q (November 3, 2009)	
	36	Regeneron SEC Form 10-Q (April 29, 2010)	
	37	Regeneron SEC Form 10-Q (July 28, 2010)	
	38	Regeneron SEC Form 10-Q (October 28, 2010)	
	39	Regeneron SEC Form 10-Q (May 3, 2011)	
	40	Regeneron SEC Form 10-Q (July 28, 2011)	
	41	Regeneron SEC Form 10-Q (October 27, 2011)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	4	of	5	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	42	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 1, 2006" (May 2, 2006)	
	43	Regeneron SEC Form 8-K Exhibit: "Press Release of Regeneron Pharmaceuticals, Inc. dated May 3, 2006" (May 5, 2006)	
	44	Regeneron SEC Form 8-K Exhibit: "Slides presented at the Company's 2006 Annual Meeting of Shareholders held on June 9, 2006" (June 9, 2006)	
	45	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 2, 2007" (May 3, 2007)	
	46	Regeneron SEC Form 8-K Exhibit: "Overheads for presentation at Regeneron's Annual Meeting of Shareholders to be held on June 8, 2007" (June 8, 2007)	
	47	Regeneron SEC Form 8-K Exhibit: "Press Release dated October 1, 2007" (October 1, 2007)	
	48	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 6, 2007" (November 6, 2007)	
	49	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 1, 2008" (May 2, 2008)	
	50	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 4, 2008" (November 4, 2008)	
	51	Regeneron SEC Form 8-K Exhibit: "99(a) Slides that Regeneron Pharmaceuticals, Inc. intends to use in conjunction with meetings with investors at the J.P. Morgan 27th Annual Healthcare Conference in San Francisco on January 12-15, 2009." (January 9, 2009)	
	52	Regeneron SEC Form 8-K Exhibit: "Press Release dated April 30, 2009" (May 1, 2009)	
	53	Regeneron SEC Form 8-K Exhibit: "Press Release dated November 3, 2009." (November 4, 2009)	
	54	Regeneron SEC Form 8-K Exhibit: "Press Release Reporting Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME) dated December 20, 2010." (December 20, 2010)	
	55	Regeneron SEC Form 8-K Exhibit: "Press Release dated February 17, 2011" (February 18, 2011)	
	56	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 April 27, 2011" (April 27, 2011)	
	57	Regeneron SEC Form 8-K Exhibit: "Press Release dated May 3, 2011." (May 3, 2011)	
	58	Regeneron SEC Form 8-K Exhibit: "Press Release, dated June 17, 2011, Announcing that EYLEA™ (aflibercept ophthalmic solution) Received Unanimous Recommendation for Approval for Treatment of Wet AMD from FDA Advisory Committee." (June 21, 2011)	
	59	Regeneron SEC Form 8-K Exhibit: "Presentation entitled VEGF Trap-Eye in CRVO: 1-year Results of the Phase 3 COPERNICUS Study" (August 22, 2011)	
	60	Regeneron SEC Form 8-K Exhibit: "Press Release Announcing FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration, dated November 18, 2011" (November 21, 2011)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/159,282
				Filing Date	October 12, 2018
				First Named Inventor	George D. Yancopoulos
				Art Unit	1647
				Examiner Name	Jon McClelland Lockard
Sheet	5	of	5	Attorney Docket Number	REGN-008CIPCON4

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	61	Regeneron Pharmaceuticals Inc., "CLEAR-IT-2: Interim Results Of The Phase II, Randomized, Controlled Dose-and Interval-ranging Study Of Repeated Intravitreal VEGF Trap Administration In Patients With Neovascular Age-related Macular Degeneration (AMD)" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	62	Regeneron Pharmaceuticals Inc., "An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients with Diabetic Macular Edema" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	63	Regeneron Pharmaceuticals Inc., "Optical Coherence Tomography Outcomes of a Phase 1, Dose-Escalation, Safety, Tolerability, and Bioactivity Study of Intravitreal VEGF Trap in Patients with Neovascular Age-Related Macular Degeneration: The CLEAR-IT 1 Study" poster presented at the 2007 Association for Research in Vision and Ophthalmology meeting in Ft. Lauderdale, Florida (May 2007)	
	64	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 (February 12, 2011)	
	65	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 (February 12, 2011)	
	66	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)	
	67	Regeneron 2008 Annual Report	
	68	Regeneron 2009 Annual Report and 10-K	
	69	Regeneron 2010 Annual Report and 10-K	
	70	RUDGE et al. "Clinical Development of VEGF Trap" In: Figg W.D., Folkman J. (eds) Angiogenesis (2008)	
	71	SCHMIDT-ERFURTH et al. "Primary Results of an International Phase III Study Using Intravitreal VEGF Trap-Eye Compared to Ranibizumab in Patients with Wet AMD (VIEW 2)" ARVO Annual Meeting Abstract (April 2011)	
	72	SLAKTER et al., "Influence of Baseline Angiographic Classification on Outcomes in the CLEAR-IT 2 Phase 2 Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration" ARVO Annual Meeting Abstract (April 2010)	
	73	SLAKTER et al., "A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration: Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) Outcomes at 1 Year" ARVO Annual Meeting Abstract (April 2009)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2005 (06.01.2005)

PCT

(10) International Publication Number
WO 2005/000895 A2

(51) International Patent Classification[7]: C07K 14/71

(21) International Application Number:
PCT/US2004/021059

(22) International Filing Date: 29 June 2004 (29.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/609,775 30 June 2003 (30.06.2003) US

(71) Applicant *(for all designated States except US)*: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DALY, Thomas, J.** [US/US]; 4 Dolphin Road, New City, NY 10956 (US). **FANDL, James, P.** [US/US]; 40 Amanda's Way, LaGrangeville, NY 12540 (US). **PAPADOPOULOS, Nicholas, J.** [US/US]; 59 Heritage Lane, LaGrangeville, NY 12540 (US).

(74) Agent: **VALETA, Gregg**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/000895 A2

(54) Title: VEGF TRAPS AND THERAPEUTIC USES THEREOF

(57) Abstract: Nucleic acid molecules and multimeric proteins capable of binding vascular endothelial growth factor (VEGF). VEGF traps are disclosed which are therapeutically useful for treating VEGF-associated conditions and diseases, and are specifically designed for local administration to specific organs, tissues, and/or cells.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1067 of 2000

VEGF TRAPS AND THERAPEUTIC USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention encompasses fusion polypeptides capable of binding vascular endothelial cell growth factor (VEGF), VEGF family members, and splice variants with specifically desirable characteristics, as well as therapeutic methods of use.

BRIEF SUMMARY OF THE INVENTION

[0002] In a first aspect, the invention features an isolated nucleic acid molecule encoding a fusion polypeptide comprising receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, wherein R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 (Flt1D2), R2 is VEGF receptor component Ig domain 3 of Flk-1 (Flk1D3), and R3 is VEGF receptor component Ig domain 3 of Flt-4 (Flt1D3 or R3), and wherein $X \geq 1$ and $Y \geq 1$.

[0003] In a related second aspect, the invention features a monomeric VEGF trap or fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$ wherein $X \geq 1$, $Y \geq 1$, and R1, R2, and R3 are as defined above. The VEGF receptor components R1, R2, and R3, may be connected directly to each other or connected via one or more spacer sequences. In one specific embodiment, the monomeric VEGF trap is $(R1R2)_X$, were X=2. In a more specific embodiment, the monomeric VEGF trap is SEQ ID NO:24, or a functionally equivalent amino acid variant thereof. The invention encompasses a monomeric VEGF trap consisting essentially of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and functionally equivalent amino acid variants thereof.

[0004] In a third aspect, the invention features an isolated nucleic acid molecule encoding a fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and a fusion partner (FP) component selected from the group consisting of a multimerizing component (MC), a serum protein, or a molecule capable of binding a serum protein. In a preferred embodiment, FP is a multimerizing component (MC) capable of interacting with a multimerizing component on another fusion polypeptide to form a multimeric structure, e.g., a dimer or trimer. Most preferably, the MC is selected from the group consisting of (i) a multimerizing component comprising a cleavable region (C-region), (ii) a truncated multimerizing component, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain. Further encompassed are fusion polypeptides consisting essentially of $(R1R2)_X$ and/or $(R1R3)_Y$, and FP. In a preferred embodiment, the fusion polypeptide consists essentially of $(R1R2)_X$ and MC.

[0005] In a fourth aspect, the invention features a fusion polypeptide comprising VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and FP, as described above. The receptor components may be arranged in different orders, for example, $(R1R2)_X$-FP; $(R1R2)_X$-FP-$(R1R2)_X$; FP-$(R2R1)_X$, etc. The components of the fusion polypeptide may be connected directly to each other, or connected via a spacer sequence.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1068 of 2000

[0006] In a fifth aspect, the invention features a VEGF trap, comprising a multimer of two or more fusion polypeptides consisting of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$, and FP, wherein the FP component is a multimerizing component (MC) comprising a C-region. The C-region may be naturally occurring or artificial, and may occur at any point within the multimerizing component, and functions to allow cleavage of a parent MC to a truncated MC. A VEGF trap composed of two or more fusion polypeptides having at least one truncated MC is termed a "truncated mini-trap."

[0007] The C-region may be created in MC by insertion, deletion, or mutation, such that an enzymatically or chemically cleavable site is created. The C-region may be created in any MC and at any position within the MC; preferably, the C-region is created in a full length Fc domain, or a fragment thereof, or a C_H3 domain. The C-region may be a site cleavable by an enzyme, such as, thrombin, ficin, pepsin, matrilysin, or prolidase or cleavable chemically by, for example, formic acid or $CuCl_2$.

[0008] In a sixth related aspect, the invention features a truncated VEGF mini-trap which is a multimeric protein comprising two or more fusion polypeptides consisting of $(R1R2)_X$ and/or $(R1R3)_Y$ and a multimerizing component which is a truncated by cleavage from a parent MC comprising a C-region (tMC).

[0009] In a seventh aspect, the invention features a fusion polypeptide consisting of VEGF receptor components $(R1R2)_X$ and/or $(R1R3)_Y$ and a MC, wherein the MC is an amino acid sequence between 1 to about 200 amino acids in length comprising at least one cysteine residue, wherein the at least one cysteine residue is capable of forming a disulfide bond with a cysteine residue present in the MC of another fusion polypeptide (cMC). In a preferred embodiment, cMC is an amino acid sequence between 1-50 amino acids in length comprising at least one cysteine residue. In a more preferred embodiment, cMC is an amino acid sequence between 1-15 amino acids in length comprising at least one amino acid. In an even more preferred embodiment, cMC is an amino acid sequence between 1-10 amino acids in length comprising 1-2 cysteine residues. One exemplification of this embodiment of the invention is shown in SEQ ID NO:27 having a signal sequence (1-26) followed by R1 (27-129) and R2 (130-231) components, followed by a nine amino acid sequence ending in a cysteine residue. In another embodiment, shown in SEQ ID NO:28, a signal sequence (1-26) is followed by R1 (27-129) and R2 (130-231) components, followed by a six amino acid sequence ending in a cysteine residue.

[0010] In an eighth aspect, the invention features a VEGF mini-trap, comprising a multimer of two or more fusion polypeptides consisting of $(R1R2)_X$ and/or $(R1R3)_Y$ and a cMC. In a more specific embodiment, the mini-trap is a dimer. One exemplification of this embodiment of the mini-trap of the invention is a dimer of the fusion polypeptide shown in SEQ ID NO:2, wherein each fusion polypeptide (R1R2-cMC) has a molecular weight of 23.0 kD and a pI of 9.22.

[0011] In another embodiment, cMC is 4 amino acids in length consisting of two cysteine residues, for example, XCXC (SEQ ID NO:3). In one exemplification of this embodiment of the invention, the mini-trap consists of the VEGF receptor components of the invention, and a cMC consisting of ACGC (SEQ ID NO:4). One exemplification of this embodiment of the mini-trap of the invention is

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1069 of 2000

a dimer of the fusion polypeptide shown in SEQ ID NO:5, wherein each monomer has a molecular weight of 23.2 kD and a pI of 9.22. Another exemplification of this embodiment of the invention is shown in SEQ ID NO:26 having a signal sequence (1-26) followed by R1 (27-129) and R2 (130-231) components, followed by a nine amino acid sequence ending in CPPC.

[0012] In all embodiments of the VEGF trap of the invention (including truncated VEGF mini-trap, VEGF mini-traps, and monomeric VEGF mini-traps), a signal sequence (S) may be included at the beginning (or N-terminus) of the fusion polypeptide of the invention. The signal sequence may be native to the cell, recombinant, or synthetic. When a signal sequence is attached to the N-terminus of a first receptor component, thus a fusion polypeptide may be designated as, for example, S-$(R1R2)_X$.

[0013] The components of the fusion polypeptide may be connected directly to each other or be connected via spacers. In specific embodiments, one or more receptor and/or fusion partner components of the fusion polypeptide are connected directly to each other without spacers. In other embodiments, one or more receptor and/or fusion partner components are connected with spacers.

[0014] The invention encompasses vectors comprising the nucleic acid molecules of the invention, including expression vectors comprising the nucleic acid molecule operatively linked to an expression control sequence. The invention further encompasses host-vector systems for the production of a fusion polypeptide which comprise the expression vector, in a suitable host cell; host-vector systems wherein the suitable host cell is a bacterial, yeast, insect, mammalian cell; an *E. coli* cell, or a COS or CHO cell. Additional encompassed are VEGF traps of the invention modified by acetylation or pegylation. Methods for acetylating or pegylating a protein are well known in the art.

[0015] In a related ninth aspect, the invention features a method of producing a VEGF trap of the invention, comprising culturing a host cell transfected with a vector comprising a nucleic acid sequence of the invention, under conditions suitable for expression of the protein from the host cell, and recovering the fusion polypeptides so produced.

[0016] The VEGF traps of the invention are therapeutically useful for treating any disease or condition which is improved, ameliorated, or inhibited by removal, inhibition, or reduction of VEGF. A non-exhaustive list of specific conditions improved by inhibition or reduction of VEGF include, for example, undesirable plasma leakage or vascular permeability, undesirable blood vessel growth, e.g., such as in a tumor, edema associated with inflammatory disorders such as psoriasis or arthritis, including rheumatoid arthritis; asthma; generalized edema associated with burns; ascites and pleural effusion associated with tumors, inflammation or trauma; chronic airway inflammation; asthma; capillary leak syndrome; sepsis; kidney disease associated with increased leakage of protein; pancreatic ductal adenocarcinoma (PDAC) and eye disorders such as age related macular degeneration and diabetic retinopathy. The VEGF mini-trap is particularly useful in treatment of eye disorders, and as an adjuvant to eye surgeries, including glaucoma surgery; and the treatment of intra-ocular tumors, such as for example, uveal melanoma, retinoblastoma, via intravitreal delivery.

[0017] Accordingly, in a tenth aspect, the invention features a therapeutic method for the treatment of a VEGF-related disease or condition, comprising administering a VEGF trap of the invention to a subject suffering from a VEGF-related disease or condition. Although any mammal

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1070 of 2000

can be treated by the therapeutic methods of the invention, the subject is preferably a human patient suffering from or at risk of suffering from a condition or disease which can be improved, ameliorated, inhibited or treated with a VEGF trap.

[0018] In a eleventh aspect, the invention further features diagnostic and prognostic methods, as well as kits for detecting, quantitating, and/or monitoring VEGF with the mini-traps of the invention.

[0019] In a twelfth aspect, the invention features pharmaceutical compositions comprising a VEGF trap of the invention with a pharmaceutically acceptable carrier. Such pharmaceutical compositions may comprise a dimeric fusion polypeptide trap, or nucleic acids encoding the fusion polypeptide. The mini-traps of the invention find specific uses in conditions in which a VEGF trap with reduced serum half life (e.g., faster clearance), and/or increased tissue penetration due to smaller size is desirable. Specific applications for the VEGF mini-trap include, for example, diseases where local administration to a specific tissue or cell is desirable. Examples of such a condition or disease are ocular diseases of the eye.

[0020] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only the appended claims.

[0022] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe the methods and/or materials in connection with which the publications are cited.

General Description

[0024] The invention encompasses a VEGF trap capable of binding and inhibiting VEGF activity which is a monomer or multimer of one or more fusion polypeptides. The molecules of the invention bind and inhibit the biological action of VEGF and/or the physiological reaction or response. For a description of VEGF-receptor-based antagonist VEGF traps Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs:7-8) and VEGFR1R2-FcΔC1(a) (SEQ ID NOs:9-10), see PCT WO/0075319, the contents of which is incorporated in its entirety herein by reference.

[0025] The mini-trap of the invention is smaller than the full sized trap, e.g., about 50 - 60 kD

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1071 of 2000

versus 120 kD of the parent trap, and include monomeric traps consisting essentially of VEGF receptor domains $(R1R2)_X$, $(R1R3)_Y$, or combinations thereof, traps generated by cleavage of a portion of a parent multimerized trap having a fusion partner component which is a multimerizing component (MC) containing a cleavage region (C-region); or by attaching a cysteine residue or amino acid sequence containing one or more cysteine residues to or between receptor component domains. In specific embodiments, the mini-trap of the invention is less than about 60 kD as measured by SDS-PAGE analysis; more preferably, about 50 kD; even more preferably about 20-30 kD; or is about 25 kD and capable of binding VEGF with an affinity comparable to a full-sized parent trap described in PCT/US00/14142.

Nucleic Acid Constructs and Expression

[0026] The present invention provides for the construction of nucleic acid molecules encoding fusion polypeptides capable of binding VEGF alone or multimerized VEGF traps. The nucleic acid molecules of the invention may encode wild-type R1, R2, and/or R3 receptor components, or functionally equivalent variants thereof. Amino acid sequence variants of the R1, R2 and/or R3 receptor components of the traps of the invention may also be prepared by creating mutations in the encoding nucleic acid molecules. Such variants include, for example, deletions from, or insertions or substitutions of, amino acid residues within the amino acid sequence of R1, R2 and/or R3. Any combination of deletion, insertion, and substitution may be made to arrive at a final construct, provided that the final construct possesses the ability to bind and inhibit VEGF.

[0027] These nucleic acid molecules are inserted into a vector that is able to express the fusion polypeptides when introduced into an appropriate host cell. Appropriate host cells include, but are not limited to, bacterial, yeast, insect, and mammalian cells. Any of the methods known to one skilled in the art for the insertion of DNA fragments into a vector may be used to construct expression vectors encoding the fusion polypeptides of the invention under control of transcriptional/translational control signals.

[0028] Expression of the nucleic acid molecules of the invention may be regulated by a second nucleic acid sequence so that the molecule is expressed in a host transformed with the recombinant DNA molecule. For example, expression may be controlled by any promoter/enhancer element known in the art. Promoters which may be used to control expression of the chimeric polypeptide molecules include, but are not limited to, a long terminal repeat (Squinto et al. (1991) Cell 65:1-20); SV40 early promoter region, CMV, M-MuLV, thymidine kinase promoter, the regulatory sequences of the metallothionine gene; prokaryotic expression vectors such as the b-lactamase promoter, or the tac promoter (see also Scientific American (1980) 242:74-94); promoter elements from yeast or other fungi such as Gal 4 promoter, ADH, PGK, alkaline phosphatase, and tissue-specific transcriptional control regions derived from genes such as elastase I.

[0029] Expression vectors capable of being replicated in a bacterial or eukaryotic host comprising the nucleic acid molecules of the invention are used to transfect the host and thereby direct expression of such nucleic acids to produce the fusion polypeptides of the invention, which form traps capable of binding to VEGF. Transfected cells may transiently or, preferably, constitutively

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1072 of 2000

and permanently express the VEGF traps of the invention.

[0030] The traps of the invention may be purified by any technique which allows for the subsequent formation of a stable, biologically active trap. For example, and not by way of limitation, the factors may be recovered from cells either as soluble proteins or as inclusion bodies, from which they may be extracted quantitatively by 8M guanidinium hydrochloride and dialysis (see, for example, US Patent No. 5,663,304). In order to further purify the factors, conventional ion exchange chromatography, hydrophobic interaction chromatography, reverse phase chromatography or gel filtration may be used.

VEGF Receptor Components

[0031] The VEGF receptor components of the VEGF mini trap consist of the Ig domain 2 of Flt-1 (Flt1D2) (R1), the Ig domain 3 of Flk-1 (Flk1D3) (R2) (together, R1R2), and/or R1 and Ig domain 3 of Flt-4 (Flt1D3) (R3) (together, R1R3). The term "Ig domain" of Flt-1, Flt-4, or Flk-1 is intended to encompass not only the complete wild-type domain, but also insertional, deletional, and/or substitutional variants thereof which substantially retain the functional characteristics of the intact domain. It will be readily apparent to one of skill in the art that numerous variants of the above Ig domains can be obtained which will retains substantially the same functional characteristics as the wild-type domain.

[0032] The term "functional equivalents" when used in reference to R1, R2, or R3, is intended to encompass an R1, R2, or R3 domain with at least one alteration, e.g., a deletion, addition, and/or substitution, which retains substantially the same functional characteristics as does the wild type R1, R2, or R3 domain, that is, a substantially equivalent binding to VEGF. It will be appreciated that various amino acid substitutions can be made in R1, R2, or R3 without departing from the spirit of the invention with respect to the ability of these receptor components to bind and inactivate VEGF. The functional characteristics of the traps of the invention may be determined by any suitable screening assay known to the art for measuring the desired characteristic. Examples of such assays are described in the experimental section below which allow determination of binding characteristics of the traps for VEGF (Kd), as well as their half-life of dissociation of the trap-ligand complex ($T_{1/2}$). Other assays, for example, a change in the ability to specifically bind to VEGF can be measured by a competition-type VEGF binding assay. Modifications of protein properties such as thermal stability, hydrophobicity, susceptibility to proteolytic degradation, or tendency to aggregate may be measured by methods known to those of skill in the art.

[0033] The components of the fusion polypeptide may be connected directly to each other or be connected via spacers. Generally, the term "spacer" (or linker) means one or more molecules, e.g., nucleic acids or amino acids, or non-peptide moieties, such as polyethylene glycol, which may be inserted between one or more component domains. For example, spacer sequences may be used to provide a desirable site of interest between components for ease of manipulation. A spacer may also be provided to enhance expression of the fusion polypeptide from a host cell, to decrease steric hindrance such that the component may assume its optimal tertiary structure and/or interact appropriately with its target molecule. For spacers and methods of identifying desirable spacers, see,

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1073 of 2000

for example, George et al. (2003) Protein Engineering 15:871-879, herein specifically incorporated by reference. A spacer sequence may include one or more amino acids naturally connected to a receptor component, or may be an added sequence used to enhance expression of the fusion polypeptides, provide specifically desired sites of interest, allow component domains to form optimal tertiary structures and/or to enhance the interaction of a component with its target molecule. In one embodiment, the spacer comprises one or more peptide sequences between one or more components which is (are) between 1-100 amino acids, preferably 1-25.

[0034] In the most specific embodiments, R1 is amino acids 27-126 of SEQ ID NO:8, or 1-126 of SEQ ID NO:8 (including the signal sequence 1-26); or amino acids 27-129 of SEQ ID NO:10, or 1-129 of SEQ ID NO:10 (including the signal sequence at 1-26). In the most specific embodiments, R2 is amino acids 127-228 of SEQ ID NO:8, or amino acids 130-231 of SEQ ID NO:10. In the most specific embodiments, R3 is amino acids 127-225 of SEQ ID NO: 13 (without a signal sequence). When, for example, R2 is placed at the N-terminus of the fusion polypeptide, a signal sequence may desirably precede the receptor component. The receptor component(s) attached to the multimerizing component may further comprise a spacer component, for example, the GPG sequence of amino acids 229-231 of SEQ ID NO:7.

Fusion Partner and Multimerizing Components

[0035] The fusion partner is any component that enhances the functionality of the fusion polypeptide. Thus, for example, an fusion partner may enhance the biological activity of the fusion polypeptide, aid in its production and/or recovery, or enhance a pharmacological property or the pharmacokinetic profile of the fusion polypeptide by, for example, enhancing its serum half-life, tissue penetrability, lack of immungenicity, or stability. In preferred embodiments, the fusion partner is selected from the group consisting of a multimerizing component, a serum protein, or a molecule capable of binding a serum protein.

[0036] When the fusion partner is a serum protein or fragment thereof, it is selected from the group consisting of α-1-microglobulin, AGP-1, orosomuciod, α-1-acid glycoprotein, vitamin D binding protein (DBP), hemopexin, human serum albumin (hSA), transferrin, ferritin, afamin, haptoglobin, α-fetoprotein thyroglobulin, α-2-HS-glycoprotein, β-2-glycoprotein, hyaluronan-binding protein, syntaxin, C1R, C1q a chain, galectin3-Mac2 binding protein, fibrinogen, polymeric Ig receptor (PIGR), α-2-macroglobulin, urea transport protein, haptoglobin, IGFBPs, macrophage scavenger receptors, fibronectin, giantin, Fc, α-1-antichyromotrypsin, α-1-antitrypsin, antithrombin III, apolipoprotein A-I, apolipoprotein B, β-2-microglobulin, ceruloplasmin, complement component C3 or C4, CI esterase inhibitor, C-reactive protein, cystatin C, and protein C. In a more specific embodiment, fusion partner is selected from the group consisting of α-1-microglobulin, AGP-1, orosomuciod, α-1-acid glycoprotein, vitamin D binding protein (DBP), hemopexin, human serum albumin (hSA), afamin, and haptoglobin. The inclusion of a fusion partner component may extend the serum half-life of the fusion polypeptide of the invention when desired. See, for example, US Patent Nos. 6,423,512, 5,876,969, 6,593,295, and 6,548,653, herein specifically incorporated by

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1074 of 2000

reference in their entirety, for examples of serum albumin fusion polypeptides. hSA is widely distributed throughout the body, particularly in the intestinal and blood components, and has an important role in the maintenance of osmolarity and plasma volume. It is slowly cleared in the liver, and typically has an *in vivo* half-life of 14-20 days in humans (Waldmann et al. (1977) Albumin, Structure Function and Uses; Pergamon Press; pp. 255-275).

[0037] When a fusion partner is a molecule capable of binding a serum protein, the molecule may be a synthetic small molecule, a lipid or liposome, a nucleic acid, including a synthetic nucleic acid such as an aptomer, a peptide, or an oligosaccharide. The molecule may further be a protein, such as, for example, FcγR1, FcγR2, FcγR3, polymeric Ig receptor (PIGR), ScFv, and other antibody fragments specific for a serum protein.

[0038] When the fusion partner is a multimerizing component (MC), it is any natural or synthetic sequence capable of interacting with another MC to form a higher order structure, e.g., a dimer, a trimer, etc. Suitable MCs may include a leucine zipper, including leucine zipper domains derived from c-jun or c-fos; sequences derived from the constant regions of kappa or lambda light chains; synthetic sequences such as helix-loop-helix motifs (Müller et al. (1998) FEBS Lett. 432:45-49), coil-coil motifs, etc., or other generally accepted multimerizing domains known to the art. In some embodiments, the fusion component comprises an immunoglobulin-derived domain from, for example, human IgG, IgM or IgA. In specific embodiments, the immunoglobulin-derived domain may be selected from the group consisting of the Fc domain of IgG, the heavy chain of IgG, and the light chain of IgG. The Fc domain of IgG may be selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group. In one example of the VEGF trap of the invention, the multimerizing component is an IgG4 Fc domain (SEQ ID NO:29).

Generation of Truncated VEGF Mini-Traps

[0039] In one embodiment of the trap of the invention, a truncated VEGF mini-trap comprising two or more fusion polypeptides of the invention, is generated by subjecting a parent trap having C-region-containing MCs to conditions under which one or more of the C-region-containing MCs is (are) cleaved. The resulting truncated mini-trap may be a full and partial cleavage product of a parent trap.

[0040] The C-region-containing MC may be any MC capable of interacting with another MC to form a higher order structure, e.g., a dimer or a trimer. The C-region may be created within an MC at any desired location. In light of the guidance provided in the examples below, one of skill in the art would be able to select a desired site for creation of a C-region based on the desired properties of the resulting truncated traps, e.g., molecular weight, monomeric or dimeric, etc.

[0041] In a specific embodiment, the C-region is a thrombin cleavage site (LVPRGS) (SEQID NO:6) inserted into an FcΔC1 domain following the N-terminal CPPC sequence (SEQ ID NO:1). In this embodiment, a full-sized parent VEGF trap construct is expressed in a cell as an Fc-tagged protein, thus allowing capture and purification by, for example, a Protein A column. Following formation of a dimer and covalent bonding between one or both of the cysteine residues of the CPPC sequence

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1075 of 2000

(SEQ ID NO:1), the dimer is exposed to thrombin under conditions which cleave one or both of the FcΔC1 domains such that truncated dimeric mini-traps are generated, having a molecular weight of approximately 50 kD – 90 kD, and has an affinity for VEGF comparable to that of the parent trap. The conditions of cleavage may be controlled by one of skill in the art to favor formation of the partial cleavage product or the fully cleaved product, the choice of cleavage conditions selected by desire for a particular product having specific properties such as molecular weight.

[0042] In a specific embodiment, the C-region is a thrombin cleavage site (LVPRGS) (SEQID NO:6) inserted into an FcΔC1 domain N-terminal to the CPPC sequence (SEQ ID NO:1). Following formation of a dimer and covalent bonding between one or both of the cysteine residues of the CPPC sequence (SEQ ID NO:1), the dimer is exposed to thrombin under conditions in which one or both of the FcΔC1 domain occur and truncated monomeric mini-traps are generated. The monomeric truncated mini-trap thus generated comprises a receptor component, and a small fragment of the Fc, and is approximately 25 kD in size and exhibits a reduced affinity for VEGF relative to the truncated dimeric trap and the full length parent trap. A similar monomeric trap produced as a recombinant protein has been shown to have a K_D of about 1 nM.

Generation of VEGF Mini-Traps

[0043] In one embodiment, the invention features VEGF mini-traps having one or more receptor component domains $(R1R2)_X$ and/or $R1R3)_Y$, wherein $X \geq 1$, $Y \geq 1$, and R1, R2, and R3 are as defined above, and optionally, a fusion partner which is preferably a MC domain which is an amino acid sequence between 1 to about 200 amino acids in length comprising at least one cysteine residue, wherein the at least one cysteine residue is capable of forming a disulfide bond with a cysteine residue present in the MC of another fusion polypeptide (cMC). The cMC may occur at the N-terminus or C-terminus of a fusion polypeptide, or between two receptor component domains. In one specific embodiment, cysteine is added to the C-terminus of a VEGF receptor component, e.g., $R1R2_C$, which allows the fusion polypeptide to form covalent dimers through formation of a covalent disulfide bond between the cysteine residue at the C-terminus of one fusion polypeptide and the cysteine residue at the C-terminus of another fusion polypeptide. In this exemplification, the mini-trap is a dimer of the fusion polypeptide shown in SEQ ID NO:2, wherein each fusion polypeptide (R1R2-cMC or $R1R2_C$) has a molecular weight of about 23.0 kD.

[0044] In another embodiment, the cMC is a sequence of 4 amino acids (XXXX) (SEQ ID NO:11) wherein X is any amino acid and the sequence comprises at least one cysteine residue. In a specific embodiment, the cMC is added to the C-terminus of a receptor component domain. In a more specific embodiment, the 4 amino acid sequence is ACGC (SEQ ID NO:4) and the cMC forms two disulfide bonds with the cysteine residues present in a second fusion polypeptide. As shown below (Table 2), both the exemplified mini-traps exhibit an affinity for VEGF comparable to the parent trap.

Therapetic Uses

[0045] The VEGF mini-traps of the invention are therapeutically useful for treating any disease or

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1076 of 2000

condition which is improved, ameliorated, inhibited or prevented by removal, inhibition, or reduction of VEGF. A non-exhaustive list of specific conditions improved by inhibition or reduction of VEGF include, clinical conditions that are characterized by excessive vascular endothelial cell proliferation, vascular permeability, edema or inflammation such as brain edema associated with injury, stroke or tumor; edema associated with inflammatory disorders such as psoriasis or arthritis, including rheumatoid arthritis; asthma; generalized edema associated with burns; ascites and pleural effusion associated with tumors, inflammation or trauma; chronic airway inflammation; capillary leak syndrome; sepsis; kidney disease associated with increased leakage of protein; and eye disorders such as age related macular degeneration and diabetic retinopathy.

[0046] The compositions of the invention are therapeutically useful for treating a wide variety of diseases associated with increased VEGF levels. For example, exaggerated Th2 inflammation and airway remodeling are characteristic in the pathogenesis of asthma (see, for example, Elias et al. (1999) J. Clin. Invest. 104:1001-6). Elevated VEGF levels have been detected in tissues and biologic samples from patients with asthma, which correlate directly with disease activity (Lee et al. (2001) J. Allergy Clin. Immunol. 107:1106-1108) and inversely with airway caliber and airway responsiveness. Further, VEGF has been postulated to contribute to asthmatic tissue edema.

[0047] Another disease associated with increased VEGF is pancreatic ductal adenocarcinoma (PDAC). This malignancy often exhibits enhanced foci of endothelial cell proliferation and frequently overexpresses VEGF (Ferrara (1999) J. Mol. Med. 77:527-543). PDAC is responsible for over 20% of deaths due to gastrointestinal malignancies, making it the fourth most common cause of cancer-related mortality in the U.S. and other industrialized countries. Experimental evidence supports an important role for VEGF in pancreatic cancer, thus a VEGF inhibitor has promise as a therapeutic to attenuate intrapancreatic tumor growth and regional and distal metastasis.

[0048] A smaller, non-glycosylated mini-trap expressed in *E. coli* (Example 4), a glycosylated mini-trap expressed in CHO cells (Example 5), or a receptor-based monomeric trap (Example 6) has optimized characteristics for local/intra-vitreal delivery, ie. a shorter serum half life for faster clearance and minimizing unwanted systemic exposure. In addition due to its smaller size, the mini-trap has the ability to penetrate through the inner-limiting membrane (ILM) in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial (RPE) layer which will help to treat retinal disease. Additionally, the mini-trap can be used for local administration for the treatment of ocular disease such as choroidal neovascularization, diabetic macular edema, proliferative diabetic retinopathy, corneal neovascularization/transplant rejection. Still further, the mini-trap can be used in any situation where transient (short-term) blocking of VEGF is required, e.g., to avoid chronic exposure to VEGF blockade, such as, for example, in the treatment of psoriasis.

[0049] A serious problem leading to failure following glaucoma surgery is early inflammation and angiogenesis, as well as too aggressive wound healing. Accordingly, the VEGF traps of the invention may be usefully employed is as an adjuvant to glaucoma surgery to prevent early hem- and lymphangiogenesis and macrophage recruitement to the filterig bleb after glaucoma surgery, and improve surgical outcome.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1077 of 2000

Combination Therapies

[0050] In numerous embodiments, a VEGF trap may be administered in combination with one or more additional compounds or therapies, including a second VEGF trap molecule, a chemotherapeutic agent, surgery, catheter devices, and radiation. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a VEGF trap and one or more additional agents; as well as administration of a VEGF trap and one or more additional agent(s) in its own separate pharmaceutical dosage formulation. For example, a VEGF trap and a cytotoxic agent, a chemotherapeutic agent or a growth inhibitory agent can be administered to the patient together in a single dosage composition such as a combined formulation, or each agent can be administered in a separate dosage formulation. Where separate dosage formulations are used, the VEGF-specific fusion polypeptide of the invention and one or more additional agents can be administered concurrently, or at separately staggered times, i.e., sequentially.

[0051] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g. I^{131}, I^{125}, Y^{90} and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

[0052] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (Cytoxan®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®;

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1078 of 2000

razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (Taxol®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (Taxotere®; Aventis Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0053] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a cancer cell either *in vitro* or *in vivo*. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), Taxol ®, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C.

Methods of Administration

[0054] The invention provides methods of treatment comprising administering to a subject an effective amount of a VEGF trap of the invention. In a preferred aspect, the trap is substantially purified (*e.g.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably a mammal, and most preferably a human.

[0055] Various delivery systems are known and can be used to administer an agent of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (e.g. daily, weekly, monthly, etc.) or in combination with other agents. Pulmonary administration can also be employed,

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1079 of 2000

e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0056] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome, in a controlled release system, or in a pump. In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), by direct injection, or by use of microparticle bombardment, or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0057] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, by injection, by means of a catheter, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, or commercial skin substitutes.

[0058] A composition useful in practicing the methods of the invention may be a liquid comprising an agent of the invention in solution, in suspension, or both. The term "solution/suspension" refers to a liquid composition where a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix. A liquid composition also includes a gel. The liquid composition may be aqueous or in the form of an ointment. Further, the composition can take the form of a solid article that can be inserted in the eye, such as for example between the eye and eyelid or in the conjunctival sac, where the VEGF trap is released. Release from such an article is usually to the cornea, either via the lacrimal fluid, or directly to the cornea itself, with which the solid article is generally in direct contact. Solid articles suitable for implantation in the eye are generally composed primarily of bioerodible or nonbioerodible polymers. An aqueous solution and/or suspension can be in the form of eye drops. A desired dosage of the active agent can be measured by administration of a known number of drops into the eye. For example, for a drop volume of 25 µl, administration of 1-6 drops will deliver 25-150 µl of the composition.

[0059] An aqueous suspension or solution/suspension useful for practicing the methods of the invention may contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers and water-insoluble polymers such as cross-linked carboxyl-containing polymers. An aqueous suspension or solution/suspension of the present invention is preferably viscous or muco-adhesive, or even more preferably, both viscous or mucoadhesive.

[0060] In another embodiment, the composition useful in practicing the methods of the invention is an *in situ* gellable aqueous composition. Such a composition comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid. Suitable

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1080 of 2000

gelling agents include but are not limited to thermosetting polymers. The term "*in situ* gellable" as used herein is includes not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid, but also includes more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye.

Diagnostic and Screening Methods

[0061] The VEGF traps of the invention may be used diagnostically and/or in screening methods. For example, the trap may be used to monitor levels of VEGF during a clinical study to evaluate treatment efficacy. In another embodiment, the methods and compositions of the present invention are used to screen individuals for entry into a clinical study to identify individuals having, for example, too high or too low a level of VEGF. The traps can be used in methods known in the art relating to the localization and activity of VEGF, *e.g.*, imaging, measuring levels thereof in appropriate physiological samples, in diagnostic methods, etc.

[0062] The traps of the invention may be used in *in vivo* and *in vitro* screening assay to quantify the amount of non-bound VEGF present, e.g., for example, in a screening method to identify test agents able to decrease the expression of VEGF. More genenerally, the traps of the invention may be used in any assay or process in which quantification and/or isolation of VEGF is desired.

Pharmaceutical Compositions

[0063] The present invention also provides pharmaceutical compositions comprising a VEGF mini-trap of the invention. Such compositions comprise a therapeutically effective amount of one or more mini-traps, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0064] The VEGF mini-trap of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1081 of 2000

[0065] Further more, aqueous compositions useful for practicing the methods of the invention have ophthalmically compatible pH and osmolality. One or more ophthalmically acceptable pH adjusting agents and/or buffering agents can be included in a composition of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, and sodium lactate; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers are included in an amount required to maintain pH of the composition in an ophthalmically acceptable range. One or more ophthalmically acceptable salts can be included in the composition in an amount sufficient to bring osmolality of the composition into an ophthalmically acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions.

[0066] The amount of the trap that will be effective for its intended therapeutic use can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. Generally, suitable dosage ranges for intravenous administration are generally about 50-5000 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0067] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0068] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0069] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Cellular Transfection and Gene Therapy

[0070] The present invention encompasses the use of nucleic acids encoding the fusion polypeptides of the invention for transfection of cells *in vitro* and *in vivo*. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells *ex vivo* and *in vivo*, through the interaction of the vector and the

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1082 of 2000

target cell. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response. An amount adequate to accomplish this is defined as "a therapeutically effective dose or amount."

[0071] In another aspect, the invention provides a method of reducing VEGF levels in a human or other animal comprising transfecting a cell with a nucleic acid encoding a fusion polypeptide of the invention, wherein the nucleic acid comprises an inducible promoter operably linked to the nucleic acid encoding the fusion polypeptide or mini-trap. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt (1998) Biotechnology 6:1149-1154.

Kits

[0072] The invention also provides an article of manufacturing comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one VEGF trap composed of two or more fusion polypeptides of the invention, and wherein the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion polypeptide can be used for treating a VEGF-mediated disease or condition.

Transgenic Animals

[0073] The invention includes transgenic non-human animals expressing a trap of the invention. A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the transgene to particular cells. A transgenic non-human animal expressing a fusion polypeptide or mini-trap of the invention is useful in a variety of applications, including as a means of producing such a fusion polypeptide.. Further, the transgene may be placed under the control of an inducible promoter such that expression of the fusion polypeptide or mini-trap may be controlled by, for example, administration of a small molecule.

Specific Embodiments

[0074] In the experiments described below, smaller VEGF traps were generated and their ability to bind VEGF was investigated. Such mini-traps are preferably uses in specific applications. For example, certain conditions or diseases may be preferably treated with local administration of a VEGF trap to a specific organ, tissue, or cell, rather than by systemic administration. In one exemplification of the mini-traps of the invention, a smaller VEGF trap was generated by directed cleavage of a dimerized VEGF trap having a cleavage region (C-region) generated in a Fc domain (Example 2). The truncated trap exhibited comparable affinity for VEGF and half-life as the full-sized parent trap. Examples 3-5 describe construction of fusion polypeptides having a VEGF receptor component and a multimerizing component consisting of one or two cysteine residues. Affinity measurements showed that the non-glycosylated fusion polypeptides expressed in *E. coli* or

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1083 of 2000

the glycosylated polypeptides expressed in CHO cells had comparable binding affinity for VEGF as the full-sized parent trap. Example 6 further illustrates a monomeric VEGF trap consisting of $(R1R2)_2$ which is capable of binding and inhibiting VEGF. Example 7 describes the construction of a VEGF mini-trap (SEQ ID NO:26) exhibiting high affinity binding for VEGF comparable to the full length trap (SEQ ID NO:10).

[0075] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0076] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Construction of Flt1D2.Flk1D3.FcΔC1(a)

[0077] The construction of a parent VEGF trap, Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs:7-8), VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10), and Flt1D2.VEGFR3D3.FcΔC1(a) (SEQ ID NOs:12-13) is described in detail in PCT publication WO/0075319, herein specifically incorporated by reference in its entirety. Also described in WO/0075319 are methods of constructing and expressing nucleic acid constructs encoding VEGF traps, methods of detecting and measuring VEGF trap binding to VEGF, methods of determining the stoichiometry of VEGF binding by BIAcore analysis, and pharmacokinetic analyses.

Example 2: Thrombin-cleaved dimeric VEGF mini-trap

[0078] The VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10) construct was modified by insertion of a thrombin cleavage following the CPPC (SEQ ID NO:1) of the Fc domain. Purified VEGF trap (5 μg) was incubated with thrombin (Novagen) in 20 mM Tris-HCl, pH 8.4, 50 mM NaCl, 2.5 mM $CaCl_2$ for 16 hrs at 37° C. Controls included cleavage control protein (CCP) and parent VEGF trap protein incubated without thrombin. SDS-PAGE analysis (Tris-Glycine 4-20% gel; 5 μg protein per lane) verified correct cleavage (results not shown).

[0079] Affinity determination. The Kd of binding of each VEGF trap to hVEGF165 was determined as described in WO/0075319, for the parent VEGF trap, uncleaved VEGF trap containing a thrombin cleavage site ("uncleaved VEGF trap"), cleaved VEGF mini-trap and recombinant monomeric R1R2-myc myc his. More specifically, the ability of the traps to block $VEGF_{165}$-dependent receptor phosphorylation was determined using primary human endothelial cells (HUVECs). $VEGF_{165}$ was incubated in the presence of varying concentrations of the test traps, and the mixture was added to

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1084 of 2000

HUVECs to stimulate tyrosine phosphorylation of VEGFR2. At sub-stoichiometric concentrations of VEGF trap, unbound VEGF induced receptor phosphorylation. However, at a 1:1 molar ratio of greater of a VEGF trap to ligand, complete blocking of receptor signaling was observed, establishing that a single molecule of a trap dimer is capable of blocking a single molecule of human $VEGF_{165}$. Thus, the high binding affinity of the VEGF trap for VEGF results in formation of a complex that prevents VEGF from interaction with cell surface receptors. Equivalent results were obtained for identical phosphorylation inhibition experiments for the parent VEGF trap, uncleaved VEGF trap, and cleaved VEGF mini-trap The results are shown in Table 1.

TABLE 1

Trap	Kinetic Dissociation Rate (1/s)	$T_{1/2}$ (hr)
parent VEGF trap	$5.51 \times 10^{-5} \pm 0.94\%$	3.5
uncleaved VEGF trap	$4.93 \times 10^{-5} \pm 0.70\%$	3.9
cleaved VEGF mini-trap	$5.46 \times 10^{-5} \pm 0.62\%$	3.53
R1R2-myc myc his monomer	$6.74 \times 10^{-3} \pm 0.38\%$	0.028

Example 3. Construction of Plasmids Encoding VEGF Mini-Traps

[0080] VEGF mini-traps were constructed from a precursor of the parent VEGF trap, VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10), in which the three amino acids glycine-alanine-proline served as a linker between the Flk1 D3 and FcΔC1(a). This plasmid, pTE115 was used in the construction of the VEGF mini-traps because the linker DNA sequence included a Srf I restriction endonuclease recognition sequence that facilitated engineering the VEGF trap. In all other respects, the VEGF trap encoded by pTE115 is identical to that of the VEGF trap, VEGFR1R2.FcΔC1(a) (SEQ ID NOs:9-10) described in detail in PCT publication WO/0075319.

[0081] Two VEGF mini-traps were constructed with multimerization domains consisting of either a single cysteine residue ($R1R2_C$) (SEQ ID NO:2) or the amino acids ACGC (SEQ ID NO:4) ($R1R2_{ACGC}$) (SEQ ID NO:5) added to the C-terminus of receptor components Flt1D2.Flk1D3. Both of these constructs are capable of forming homo-dimeric molecules stabilized by one ($R1R2_C$) or two ($R1R2_{ACGC}$) intermolecular disulfides.

[0082] The plasmid pTE517 was made by removing the 690 bp fragment generated by digestion of pTE115 DNA with Srf I and Not I and inserting the synthetic DNA fragment formed by annealing the oligos R1R2NC (SEQ ID NO:14) and R1R2CC (SEQ ID NO:15). The resulting plasmid encodes $R1R2_C$, which consists of the Flt1D2.Flk1D3 domains followed by a cysteine residue (SEQ ID NO:23). Similarly, the plasmid pTE518 was made by removing the 690 bp fragment generated by digestion of pTE115 DNA with Srf I and Not I, followed by ligation with the synthetic DNA fragment formed by annealing the oligos R1R2NACGC (SEQ ID NO:16) and R1R2CACGC (SEQ ID NO:17). The resulting plasmid encodes $R1R2_{ACGC}$, which consists of the Flt1D2.Flk1D3 domains followed by the amino acids ACGC (SEQ ID NO:25).

[0083] Plasmids were also constructed to direct the expression of these mini-traps in *E. coli*. The primers R1R2N-Nco1 (SEQ ID NO:18) and R1R2CNot1 (SEQ ID NO:19) were used to amplify a DNA fragment from pTE115 that encodes amino acids G30 to K231, relative to the parental VEGF trap (SEQ ID NO:10). Amplification of this sequence resulted in fusion of an initiating methionine

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1085 of 2000

codon at the 5' end and fusion of the codon for cysteine, followed by a stop codon, at the 3' end (SEQ ID NO:2). This DNA fragment was then cloned into the Nco I and Not I sites of the *E. coli* expression plasmid pRG663 to yield pRG1102 such that expression of $R1R2_C$ was dependent on transcription from the phage T7 Φ1.1 promoter. Induction of gene expression from pRG1102 results in accumulation of R1R2cys in the cytoplasm of the *E. coli* host strain RFJ238. Similarly, the primers R1R2N-Nco1 (SEQ ID NO:18) and R1R2ACGC-N ot1 (SEQ ID NO:20) were used to amplify a DNA fragment from pTE115 that encodes amino acids G30 to K231 (SEQ ID NO:10) resulting in fusion of an initiating methionine codon at the 5' end and fusion of codons for ACGC (SEQ ID NO:4), followed by a stop codon, at the 3' end (SEQ ID NO:5). This fragment was then cloned into the Nco I and Not I sites of the *E. coli* expression plasmid pRG663 to yield pRG1103 such that expression of $R1R2_{ACGC}$ was dependent on transcription from the phage T7 Φ1.1 promoter. Induction of gene expression from both pRG1102 and pRG1103 resulted in accumulation of $R1R2_C$ or $R1R2_{ACGC}$, respectively, in the cytoplasm of the *E. coli* host strain RFJ238.

Example 4. Purification and characterization of VEGF mini-traps from *E. coli*

[0084] Both $R1R2_C$ and $R1R2_{ACGC}$ were expressed as cytoplasmic proteins in *E. coli* and were purified by the same method. Induction of the phage T7 Φ1.1 promoter on either pRG1102 or pRG1103 in the *E. coli* K12 strain RFJ238 resulted in accumulation of the protein in the cytoplasm. After induction, cells were collected by centrifugation, resuspended in 50 mM Tris-HCl, pH 7.5, 20 mM EDTA, and lysed by passage through a Niro-Soavi cell homogenizer. Inclusion bodies were collected from lysed cells by centrifugation, washed once in distilled H_2O, then solubilized in 8 M guanidinium-HCl, 50 mM Tris-HCl, pH 8.5, 100 mM sodium sulfite,10 mM sodium tetrathionate and incubated at room temperature for 16 hours. Clarified supernatant was fractionated on an S300 column equilibrated with 6 M guanidinium-HCl, 50 mM Tris-HCl, pH 7.5. Fractions containing $R1R2_C$ were pooled and dialyzed against 6M Urea, 50 mM Tris-HCl, pH 7.5. Dialyzed protein was diluted to 2M Urea, 50 mM Tris-HCl, pH 8.5, 2 mM cysteine then stirred slowly for 7 days at 4°C. Refolded protein was dialyzed against 50 mM Tris-HCl, pH 7.5 then loaded onto an SP-sepharose column equilibrated with 50 mM Tris-HCl, pH 7.5 and eluted with a NaCl gradient from 0 to 1 M in 50 mM Tris-HCl, pH 7.5. Fractions containing $R1R2_C$ were pooled, concentrated, and loaded onto a Superdex 200 column equilibrated with 50 mM Tris-HCl, pH 7.5, 150 mM NaCl. Fractions containing mini-trap dimer were collected and pooled. The molecular weight of purified mini-trap was estimated to be about 46 kD by SDS-PAGE.

[0085] BIAcore assays were conducted (as described in WO/0075319) to determine trap affinity for VEGF, and the results showed that the $R1R2_C$ and $R1R2_{ACGC}$ mini-traps had VEGF affinity comparable to the full length VEGF trap (Table 2).

TABLE 2

Trap	Kinetic Dissociation Rate (1/s)	$T_{1/2}$ (hr)
VEGF trap	4.23×10^{-5}	4.53
$R1R2_C$	3.39×10^{-5}	5.68
$R1R2_{ACGC}$	3.41×10^{-5}	5.65

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1086 of 2000

Example 5. Expression of VEGF mini-traps in CHO K1

[0086] Expression of the VEGF mini-traps encoded by pTE517 and pTE518 is dependent on transcription from the human CMV-MIE promoter and results in secretion of the mini-traps into the culture medium when expressed in CHO cells. When expressed as secreted proteins in CHO K1, both mini-traps were found in the conditioned media and estimation of their molecular weight by SDS-PAGE suggested, as expected, that the proteins were glycosylated. Analysis by SDS-PAGE also indicated that the mini-traps were capable of forming homo-dimeric molecules stabilized by intermolecular disulfide(s) between the C-terminal cysteine(s). Specifically, the $R1R2_C$ mini-trap efficiently formed covalent dimers when expressed as a secreted protein in CHO cells.

Example 6. Construction and expression of a single chain VEGF mini-trap

[0087] A VEGF mini-trap was also constructed that did not require a multimerization domain (SEQ ID NO:24). This mini-trap was constructed by direct fusion of one Flt1D2.Flk1D3 domain (R1R2) (amino acids 30-231 of SEQ ID NO:24) to a second Flt1D2.Flk1D3 domain (R1R2) (amino acids 234-435 of SEQ ID NO:24) with a Gly-Pro linker between the tandem receptor domains (amino acids 232-233 of SEQ ID NO:24).

[0088] To construct a gene encoding tandem Flt1D2.Flk1D3 domains, a DNA fragment was synthesized (Blue Heron Biotechnology) that encoded one Flt1D2.Flk1D3 domain that minimized DNA homology with the Flt1D2.Flk1D3 domain-encoding DNA found in pTE115. This synthetic DNA fragment was cloned as a Srf I-Not I fragment into the Srf I-Not I sites of pTE115 to yield pTE570, which expresses the R1R2-R1R2 VEGF mini-trap from the CMV-MIE promoter. When this plasmid is transfected into CHO K1 cells the R1R2-R1R2 VEGF mini-trap accumulates in the culture medium.

Example 7. Construction and expression of a VEGF mini-trap

[0089] A VEGF mini-trap was constructed as described above, by direct fusion of one Flt1D2.Flk1D3 domain (R1R2) (amino acids 30-231 of SEQ ID NO:26) with a C-terminal nine amino acid sequence terminating in CPPC. When this plasmid is transfected into CHO K1 cells the VEGF mini-trap of SEQ ID NO:26 is secreted into the culture medium. Subsequent purification by non-reducing SDS-PAGE electrophoresis as well as native light-scattering analysis identified a trap molecule with molecular weight approximately 64 kDa. This molecular weight indicates that a covalent dimer was formed between two fusion polypeptides of SEQ ID NO:26. Similar experiments were conducted with plasmids encoding the fusion polypeptides of SEQ ID NOS:27 and 28, and similarly showed these molecules formed homodimeric traps. Affinity determinations for human VEGF-165 binding to EGF traps composed of dimers of SEQ ID NO:10 and SEQ ID NO:26 are shown in Table 3.

TABLE 3

VEGF Trap	ka (1/Ms)	kd (1/s)	KD (M)
SEQ ID NO:10	$2.73 \times 10^{+7}$	1.79×10^{-5}	6.55×10^{-13}
SEQ ID NO:26	$2.00 \times 10^{+7}$	6.56×10^{-6}	3.28×10^{-13}
SEQ ID NO:26	$2.61 \times 10^{+7}$	5.77×10^{-6}	2.21×10^{-13}

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1087 of 2000

We claim:

1. An isolated nucleic acid molecule encoding a fusion polypeptide consisting of components $(R1R2)_X$ or $(R1R3)_Y$, and a fusion partner (FP), wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4.

2. The isolated nucleic acid of claim 1, wherein the fusion partner (FP) is a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure.

3. The isolated nucleic acid of claim 3, wherein the MC is selected from the group consisting of (i) a multimerizing component comprising a cleavable region (C-region), (ii) a truncated multimerizing component, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

4. A fusion polypeptide encoded by the nucleic acid molecule of claims 1 to 3.

5. The fusion polypeptide of claim 4, having the amino acid sequence of SEQ ID NO:26, 27, or 28.

6. A replicable expression vector capable in a transformed host cell comprising the nucleic acid molecule of claims 1 to 3.

7. A method of producing a VEGF fusion polypeptide, comprising the steps of introducing into a suitable expression system the expression vector of claim 6, and effecting expression of the VEGF fusion polypeptide.

8. A vascular endothelial cell growth factor (VEGF) trap, comprising a multimer of two or more fusion polypeptides of claim 4.

9. The VEGF trap of claim 8, which is a dimer.

10. A dimeric VEGF trap comprising two fusion polypeptides comprising the amino acid sequence of SEQ ID NO:26, 27, or 28.

11. A pharmaceutical composition comprising the fusion polypeptide of claims 8 or 9, and a pharmaceutically acceptable carrier.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1088 of 2000

12. A method of treating a disease or condition which is improved, ameliorated, or inhibited by removal or inhibition of vascular endothelial growth factor (VEGF), comprising administering the pharmaceutical composition of claim 11 to a subject in need thereof.

13. The method of claim 12, wherein the disease or condition is an ocular disease or condition.

14. The method of claim 13, wherein the ocular disease or condition is age related macular degeneration.

15. An isolated nucleic acid molecule encoding a fusion polypeptide consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4, wherein the multimerizing component (MC) is selected from the group consisting of (i) a MC comprising a cleavable region (C-region), (ii) a truncated MC, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

16. The isolated nucleic acid molecule of claim 15, wherein the receptor components are $(R1R2)_X$ and the multimerizing component is an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue.

17. The isolated nucleic acid molecule of claim 16, wherein the receptor component is R1R2, X is 1, and the multimerizing component is an amino acid sequence 1-15 amino acids in length with 1-2 cysteine residues.

18. A fusion polypeptide capable of binding vascular endothelial growth factor (VEGF) encoded by the nucleic acid molecule of claims 15 to 17.

19. The fusion polypeptide of claim 18, comprising the amino acid sequence of SEQ ID NO:26, 27 or 28.

20. A fusion polypeptide consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 and R2 is Ig domain 3 of Flk-1, R3 is Ig domain 3 of Flt-4, wherein the multimerizing component (MC) is selected from the group consisting of (i) a MC comprising a cleavable region (C-region), (ii) a truncated MC, (iii) an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue, (iv) a leucine zipper, (v) a helix loop motif, (vi) a coil-coil motif, and (vii) an immunoglobulin domain.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1089 of 2000

21. The fusion polypeptide of claim 20, wherein the receptor components are $(R1R2)_X$ and the multimerizing component is an amino acid sequence between 1 to about 200 amino acids in length having at least one cysteine residue.

22. The fusion polypeptide of claim 21, wherein the receptor component is R1R2, X is 1, and the multimerizing component is an amino acid sequence 1-15 amino acids in length with 1-2 cysteine residues.

23. A dimeric VEGF trap composed of two of the fusion polypeptides of claims 20 to 22.

24. An article of manufacturing comprising:

(a) packaging material; and

(b) a pharmaceutical agent contained within said packaging material;

wherein the pharmaceutical agent comprises at least one VEGF trap consisting of receptor components $(R1R2)_X$ or $(R1R3)_Y$, and a multimerizing component (MC) capable of interacting with another MC to form a multimeric structure, wherein $X \geq 1$, $Y \geq 1$, and wherein the packaging material comprises a label or package insert which indicates that said VEGF-specific fusion polypeptide can be used for treating a VEGF-mediated disease or condition.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1090 of 2000

SEQUENCE LISTING

<110> Daly, Thomas J.
Fandl, James P.
Papadopoulos, Nicholas J.

<120> VEGF TRAPS AND THERAPEUTIC USES THEREOF

<130> 710D2-WO

<140> to be assigned
<141> 2004-06-29

<150> 10/609,775
<151> 2003-06-30

<160> 29

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 4
<212> PRT
<213> homo sapiens

<400> 1
Cys Pro Pro Cys
1

<210> 2
<211> 200
<212> PRT
<213> homo sapiens

<400> 2
Met Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile
1 5 10 15
His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser
20 25 30
Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile
35 40 45
Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile
50 55 60
Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr
65 70 75 80
Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr Gln Thr Asn Thr
85 90 95
Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val
100 105 110
Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val
115 120 125
Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys
130 135 140
Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys
145 150 155 160
Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln
165 170 175
Gly Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
180 185 190

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1091 of 2000

```
Phe Val Arg Val His Glu Lys Cys
        195                 200

<210> 3
<211> 4
<212> PRT
<213> homo sapiens

<220>
<221> VARIANT
<222> 1, 3
<223> Xaa = Any Amino Acid

<400> 3
Xaa Cys Xaa Cys
 1

<210> 4
<211> 4
<212> PRT
<213> homo sapiens

<400> 4
Ala Cys Gly Cys
 1

<210> 5
<211> 203
<212> PRT
<213> homo sapiens

<400> 5
Met Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile
 1               5                  10                  15
His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser
            20                  25                  30
Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile
        35                  40                  45
Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile
    50                  55                  60
Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr
65                  70                  75                  80
Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr Gln Thr Asn Thr
                85                  90                  95
Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val
            100                 105                 110
Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val
        115                 120                 125
Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys
    130                 135                 140
Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys
145                 150                 155                 160
Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln
                165                 170                 175
Gly Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
            180                 185                 190
Phe Val Arg Val His Glu Lys Ala Cys Gly Cys
        195                 200

<210> 6
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1092 of 2000

<211> 6
<212> PRT
<213> homo sapiens

<400> 6
Leu Val Pro Arg Gly Ser
1 5

<210> 7
<211> 1453
<212> DNA
<213> homo sapiens

<400> 7
aagcttgggc tgcaggtcga tcgactctag aggatcgatc cccgggcgag ctcgaattcg 60
caaccaccat ggtcagctac tgggacaccg gggtcctgct gtgcgcgctg ctcagctgtc 120
tgcttctcac aggatctagt tccggaggta gacctttcgt agagatgtac agtgaaatcc 180
ccgaaattat acacatgact gaaggaaggg agctcgtcat tccctgccgg gttacgtcac 240
ctaacatcac tgttacttta aaaaagtttc cacttgacac tttgatccct gatggaaaac 300
gcataatctg ggacagtaga aagggcttca tcatatcaaa tgcaacgtac aaagaaatag 360
ggcttctgac ctgtgaagca acagtcaatg ggcatttgta taagacaaac tatctcacac 420
atcgacaaac caatacaatc atagatgtgg ttctgagtcc gtctcatgga attgaactat 480
ctgttggaga aaagcttgtc ttaaattgta cagcaagaac tgaactaaat gtggggattg 540
acttcaactg ggaataccct tcttcgaagc atcagcataa gaaacttgta aaccgagacc 600
taaaaaccca gtctgggagt gagatgaaga aatttttgag caccttaact atagatggtg 660
taacccggag tgaccaagga ttgtacacct gtgcagcatc cagtgggctg atgaccaaga 720
agaacagcac atttgtcagg gtccatgaaa agggcccggg cgacaaaact cacacatgcc 780
caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac 840
ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga 900
gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg 960
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca 1020
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag 1080
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac 1140
aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc agcctgacct 1200
gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1260
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcttcctct 1320
atagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1380
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta 1440
aatgagcggc cgc 1453

<210> 8
<211> 458
<212> PRT
<213> homo sapiens

<400> 8
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Gly Arg Pro Phe Val Glu
20 25 30
Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu
35 40 45
Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
50 55 60
Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
65 70 75 80
Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
85 90 95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
100 105 110

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1093 of 2000

```
Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val
        115                 120                 125
Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val
    130                 135                 140
Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn
145                 150                 155                 160
Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg
                165                 170                 175
Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr
            180                 185                 190
Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys
        195                 200                 205
Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg
    210                 215                 220
Val His Glu Lys Gly Pro Gly Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
<210> 9
<211> 1377
<212> DNA
<213> homo sapiens

<400> 9
atggtcagct actgggacac cggggtcctg ctgtgcgcgc tgctcagctg tctgcttctc 60
acaggatcta gttccggaag tgataccggt agacctttcg tagagatgta cagtgaaatc 120
cccgaaatta tacacatgac tgaaggaagg gagctcgtca ttccctgccg ggttacgtca 180
cctaacatca ctgttacttt aaaaaagttt ccacttgaca ctttgatccc tgatggaaaa 240
cgcataatct gggacagtag aaagggcttc atcatatcaa atgcaacgta caaagaaata 300
gggcttctga cctgtgaagc aacagtcaat gggcatttgt ataagacaaa ctatctcaca 360
catcgacaaa ccaatacaat catagatgtg gttctgagtc cgtctcatgg aattgaacta 420
tctgttggag aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt 480
gacttcaact gggaataccc ttcttcgaag catcagcata agaaacttgt aaaccgagac 540
ctaaaaaccc agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt 600
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1094 of 2000

```
gtaacccgga gtgaccaagg attgtacacc tgtgcagcat ccagtgggct gatgaccaag 660
aagaacagca catttgtcag ggtccatgaa aaggacaaaa ctcacacatg cccaccgtgc 720
ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 780
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 840
gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 900
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 960
caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 1020
gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 1080
accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1140
aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 1200
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1260
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1320
gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga    1377
```

<210> 10
<211> 458
<212> PRT
<213> homo sapiens

<400> 10

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1095 of 2000

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

<210> 11
<211> 4
<212> PRT
<213> homo sapiens

<220>
<221> VARIANT
<222> 1, 2, 3, 4
<223> Xaa = Any Amino Acid

<400> 11
Xaa Xaa Xaa Xaa
 1

<210> 12
<211> 1444
<212> DNA
<213> homo sapiens

<400> 12

```
aagcttgggc tgcaggtcga tcgactctag aggatcgatc cccgggcgag ctcgaattcg 60
caaccaccat ggtcagctac tgggacaccg gggtcctgct gtgcgcgctg ctcagctgtc 120
tgcttctcac aggatctagt tccggaggta gacctttcgt agagatgtac agtgaaatcc 180
ccgaaattat acacatgact gaaggaaggg agctcgtcat tccctgccgg gttacgtcac 240
ctaacatcac tgttacttta aaaaagtttc cacttgacac tttgatccct gatggaaaac 300
gcataatctg ggacagtaga aagggcttca tcatatcaaa tgcaacgtac aaagaaatag 360
ggcttctgac ctgtgaagca acagtcaatg ggcatttgta taagacaaac tatctcacac 420
atcgacaaac caatacaatc atagatatcc agctgttgcc caggaagtcg ctggagctgc 480
tggtagggga gaagctggtc ctcaactgca ccgtgtgggc tgagtttaac tcaggtgtca 540
cctttgactg ggactaccca gggaagcagg cagagcgggg taagtgggtg cccgagcgac 600
gctcccaaca gacccacaca gaactctcca gcatcctgac catccacaac gtcagccagc 660
acgacctggg ctcgtatgtg tgcaaggcca acaacggcat ccagcgattt cgggagagca 720
ccgaggtcat tgtgcatgaa aatggcccgg gcgacaaaac tcacacatgc ccaccgtgcc 780
cagcacctga actcctgggg ggaccgtcag tcttcctctt cccccaaaa cccaaggaca 840
ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg agccacgaag 900
accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat gccaagacaa 960
agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc accgtcctgc 1020
accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag 1080
cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca caggtgtaca 1140
ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc tgcctggtca 1200
aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag ccggagaaca 1260
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1096 of 2000

actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc tatagcaagc 1320
tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg 1380
aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt aaatgagcgg 1440
ccgc 1444

<210> 13
<211> 455
<212> PRT
<213> homo sapiens

<400> 13
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Gly Arg Pro Phe Val Glu
20 25 30
Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu
35 40 45
Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
50 55 60
Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
65 70 75 80
Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
85 90 95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
100 105 110
Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Ile Gln
115 120 125
Leu Leu Pro Arg Lys Ser Leu Glu Leu Leu Val Gly Glu Lys Leu Val
130 135 140
Leu Asn Cys Thr Val Trp Ala Glu Phe Asn Ser Gly Val Thr Phe Asp
145 150 155 160
Trp Asp Tyr Pro Gly Lys Gln Ala Glu Arg Gly Lys Trp Val Pro Glu
165 170 175
Arg Arg Ser Gln Gln Thr His Thr Glu Leu Ser Ser Ile Leu Thr Ile
180 185 190
His Asn Val Ser Gln His Asp Leu Gly Ser Tyr Val Cys Lys Ala Asn
195 200 205
Asn Gly Ile Gln Arg Phe Arg Glu Ser Thr Glu Val Ile Val His Glu
210 215 220
Asn Gly Pro Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
355 360 365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1097 of 2000

```
385                 390                 395                 400
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445
Leu Ser Leu Ser Pro Gly Lys
    450                 455
```

<210> 14
<211> 24
<212> DNA
<213> homo sapiens

<400> 14
gggctgttga gagagagaga gagc 24

<210> 15
<211> 28
<212> DNA
<213> homo sapiens

<400> 15
ggccgctctc tctctctctc aacagccc 28

<210> 16
<211> 23
<212> DNA
<213> homo sapiens
<400> 16
gggcgcatgc ggttgttgag agc 23

<210> 17
<211> 27
<212> DNA
<213> homo sapiens

<400> 17
ggccgctctc aacaaccgca tgcgccc 27

<210> 18
<211> 36
<212> DNA
<213> homo sapiens

<400> 18
gagagagacc atgggtagac ctttcgtaga gatgta 36

<210> 19
<211> 48
<212> DNA
<213> homo sapiens

<400> 19
agagaggcgg ccgctttatc aacacttttc atggaccctg acaaatgt 48

<210> 20
<211> 57
<212> DNA

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1098 of 2000

<213> homo sapiens

<400> 20
agagaggcgg ccgctttatc aacaaccgca tgccttttca tggaccctga caaatgt 57

<210> 21
<211> 39
<212> DNA
<213> homo sapiens

<400> 21
agttccggaa gtgccatggg tagacctttc gtagagatg 39

<210> 22
<211> 44
<212> DNA
<213> homo sapiens

<400> 22
agagaggcgg ccgctgttat cacttctcgt gcacgcgcac gaag 44

<210> 23
<211> 235
<212> PRT
<213> homo sapiens

<400> 23
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65 70 75 80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
130 135 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145 150 155 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
165 170 175
Val Asn Thr Gln Ser Gly Ser Glu Met Lys Arg Asp Leu Lys Lys Phe
180 185 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
195 200 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
210 215 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Cys
225 230 235

<210> 24
<211> 435

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1099 of 2000

<212> PRT
<213> homo sapiens

<400> 24

```
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Arg Pro Phe Val Glu Met
225                 230                 235                 240
Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu
                245                 250                 255
Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys
            260                 265                 270
Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp
        275                 280                 285
Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile
    290                 295                 300
Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr
305                 310                 315                 320
Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu
                325                 330                 335
Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu
            340                 345                 350
Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp
        355                 360                 365
Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp
    370                 375                 380
Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu
385                 390                 395                 400
Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala
                405                 410                 415
Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val
            420                 425                 430
His Glu Lys
        435
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1100 of 2000

<210> 25
<211> 238
<212> PRT
<213> homo sapiens

<400> 25
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asn Thr Leu Ile Pro Asn Gly Lys
65 70 75 80
Ala Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
130 135 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145 150 155 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
165 170 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
180 185 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
195 200 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
210 215 220
Phe Val Arg Val His Glu Lys Gly Pro Gly Ala Cys Gly Cys
225 230 235

<210> 26
<211> 240
<212> PRT
<213> homo sapiens

<400> 26
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
20 25 30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65 70 75 80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1101 of 2000

```
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240

<210> 27
<211> 240
<212> PRT
<213> homo sapiens

<400> 27
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Ser Pro Pro Cys
225                 230                 235                 240

<210> 28
<211> 237
<212> PRT
<213> homo sapiens

<400> 28
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1               5                  10                  15
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1102 of 2000

```
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
            20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
        35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys
225                 230                 235
```

<210> 29
<211> 434
<212> PRT
<213> homo sapiens

```
<400> 29
Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
 1               5                  10                  15
Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
            20                  25                  30
Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
        35                  40                  45
Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
    50                  55                  60
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
65                  70                  75                  80
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
                85                  90                  95
Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile
            100                 105                 110
Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr
        115                 120                 125
Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys
    130                 135                 140
His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly
145                 150                 155                 160
Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr
                165                 170                 175
Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met
            180                 185                 190
Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys Glu Ser Lys
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1103 of 2000

```
     195                 200                 205
Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
    210                 215                 220
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
225                 230                 235                 240
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
                245                 250                 255
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
            260                 265                 270
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
        275                 280                 285
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
    290                 295                 300
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
305                 310                 315                 320
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                325                 330                 335
Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
            340                 345                 350
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
        355                 360                 365
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
    370                 375                 380
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
385                 390                 395                 400
Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
                405                 410                 415
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
            420                 425                 430
Gly Lys
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1104 of 2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/106378 A2

(51) International Patent Classification[7]: C07K 16/24, A61K 31/7088, C07K 19/00, 14/71

(21) International Application Number: PCT/US2004/012540

(22) International Filing Date: 23 April 2004 (23.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/473,734 28 May 2003 (28.05.2003) US
60/492,865 6 August 2003 (06.08.2003) US

(71) Applicants *(for all designated States except US)*: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **THE SCHEPENS EYE RESEARCH INSTITUTE** [US/US]; 20 Staniford Street, Boston, MA 021114 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WIEGAND, Stanley** [US/US]; 15 Fox Run Road, Croton on Hudson, NY 10520 (US). **CAO, Jingtai** [CN/US]; 308 N. Greeley Avenue, Chappaqua, NY 10514 (US). **CURSIEFEN, Claus** [DE/DE]; Nordliche Stadtmauerstr. 14, 91054 Erlangen (DE).

(74) Agent: **VALETA, Gregg**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/106378 A2

(54) Title: METHOD OF TREATING CORNEAL TRANSPLANT REJECTION

(57) Abstract: Methods of preventing, reducing, or treating corneal transplant rejection to improve transplant survival in a subject in need thereof comprising administering an agent capable of blocking or inhibiting vascular endothelial growth factor (VEGF) are provided. The methods are useful for inhibiting or preventing corneal transplant rejection in a human subject who is the recipient of a transplanted cornea.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1105 of 2000

METHOD OF TREATING CORNEAL TRANSPLANT REJECTION

BACKGROUND

Field of the Invention

[0001] The field of the invention is related to methods of using VEGF antagonists to reduce, prevent, or treat corneal transplant rejection, thus improving long-term transplant survival.

Description of Related Art

[0002] It has previously been reported that topical application of an anti-VEGF neutralizing antibody suppresses acute allograft rejection in a rat corneal transplant model (Yatoh et al. (1998) Transplantation 66(11):1519-24). As the leading cause of human corneal transplant failure is transplant rejection, there is a need for a therapeutic for use in preventing corneal transplant rejection in humans who receive a corneal transplant.

BRIEF SUMMARY OF THE INVENTION

[0003] The invention is based in part on the finding that administration of an agent capable of blocking or inhibiting vascular endothelial growth factor (VEGF) prevents corneal transplant rejection. The experiments, described below, conducted in an animal model of corneal transplantation show that long-term transplant survival is promoted by blocking VEGF-mediated activity.

[0004] In a first aspect, the invention features a method of improving transplant survival in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that transplant survival is improved.

[0005] In specific embodiments, the agent capable of blocking, inhibiting, or ameliorating VEGF-mediated activity is a VEGF antagonist. The VEGF antagonist may be a polypeptide, an antibody, a small molecule, or a nucleic acid. More specifically, the VEGF antagonist includes a VEGF trap selected from the group consisting of acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a). In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2. The invention encompasses the use of a VEGF trap that is at least 90%, 95%, 98%, or at least 99%

homologous with the nucleotide sequence set forth in SEQ ID NO: 1 and/or the amino acid sequence set forth in SEQ ID NO:2.

[0006] In other embodiments, the agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity is a nucleic acid-based antagonist capable of interfering with the expression of VEGF. A specific example of this embodiment is one in which the nucleic acid-based antagonist is an aptamer, an siRNA, or an antisense molecule.

[0007] Administration of the agent may be by any method known in the art, including subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, oral, or topical routes of administration. Preferable, administration to the subject in need of the agent is topical administration to the eye or subconjunctival administration. Administration may occur prior to or following corneal transplantation, preferably following surgery. Administration may also include a second agent, such as an immunosuppressive agent.

[0008] The subject to be treated is preferably a human subject who has or will receive a corneal transplant.

[0009] In a related second aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for improving transplant survival in a mammalian subject.

[0010] In a third aspect, the invention features a method of preventing corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that corneal transplant rejection is prevented.

[0011] In a related fourth aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for the treatment of corneal transplant rejection in a mammalian subject.

[0012] In a fifth aspect, the invention features a method of reducing the incidence of corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that the incidence of corneal transplant rejection is reduced.

[0013] In a related sixth aspect, the invention features the use of an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for reducing the incidence of corneal transplant rejection in a mammalian subject receiving a corneal transplant.

[0014] In a seventh aspect, the invention features a pharmaceutical composition comprising a VEGF antagonist, for example the VEGF trap VEGFR1R2-FcΔC1(a), in a pharmaceutically

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1107 of 2000

acceptable carrier. Such pharmaceutical compositions may be liquid, gel, ointment, salve, slow release formulations or other formulations suitable for ophthalmic administration.

[0015] In an eighth aspect, the invention features an article of manufacture comprising packaging materials and a pharmaceutical agent contained within the packaging materials, wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention, and the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion protein can be used for the treatment or prevention of corneal transplant rejection.

[0016] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0017] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0018] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

General Description

[0020] Experiments were undertaken to evaluate occurrence and time course of hem- and lymphangiogenesis after normal-risk corneal transplantation and to test whether pharmacologic strategies inhibiting both processes improve long-term graft survival. As described in the experimental section below, normal-risk allogeneic (C57BL/6 to BALB/c) and syngeneic (BALB/c to BALB/c) corneal transplantations were performed and occurrence and time course

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1108 of 2000

of hem- and lymphangiogenesis after keratoplasty was observed using double immunofluorescence of corneal flatmounts (with CD31 as panendothelial and LYVE-1 as lymphatic vascular endothelial specific marker). A molecular trap designed to eliminate VEGF-A ("VEGF $Trap_{R1R2}$"; 12.5 mg/kg) was tested for its ability to inhibit both processes after keratoplasty and to promote long-term graft survival (intraperitoneal injections on the day of surgery and 3, 7, and 14 days later). The results show that no blood or lymph vessels were detectable immediately after normal-risk transplantation in either donor or host cornea, but hem- and lymphangiogenesis were clearly visible at day 3 after transplantation. Both vessel types reached donor tissue at one week after allo- and similarly after syngeneic grafting. Early postoperative trapping of VEGF-A significantly reduced both hem- and lymphangiogenesis and significantly improved long-term graft survival (78% versus 40%; $p<0.05$). There is concurrent, VEGF-A-dependent hem- and lymphangiogenesis after normal-risk keratoplasty within the preoperatively avascular recipient bed. Inhibition of hem- and lymphangiogenesis (which mediate the efferent and afferent arms of an immune response) after normal-risk corneal transplantation improves long-term graft survival, establishing that early postoperative hem- and lymphangiogenesis are risk factors for graft rejection even in low-risk eyes.

Definitions

[0021] By the term "therapeutically effective dose" is meant a dose that produces the desired effect for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0022] By the term "blocker", "inhibitor", or "antagonist" is meant a substance that retards or prevents a chemical or physiological reaction or response. Common blockers or inhibitors include but are not limited to antisense molecules, antibodies, antagonists and their derivatives. More specifically, an example of a VEGF blocker or inhibitor is a VEGF receptor-based antagonist including, for example, an anti-VEGF antibody, or a VEGF trap such as VEGFR1R2-FcΔC1(a) (SEQ ID NOs:1-2). For a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a), see PCT publication WO/00/75319, the contents of which is incorporated in its entirety herein by reference.

[0023] A "small molecule" is defined herein to have a molecular weight below about 500 Daltons, and may include chemical as well as peptide molecules.

VEGF Antagonists

[0024] In one aspect of the invention, VEGF-mediated activity is blocked or inhibited by the use

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1109 of 2000

of VEGF receptor-based blockers of VEGF-mediated activity. A non-limiting example of a VEGF receptor-based blocker includes, but is not limited to, VEGFR1R2-FcΔC1(a). Other suitable receptor-based blockers include acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a). For a complete description of these and other VEGF-receptor-based blockers, including pegylated receptor-based blockers, see PCT Publication No. WO/00/75319, the contents of which is incorporated in its entirety herein by reference.

[0025] In addition to the VEGF receptor-based blockers described in PCT Publication No. WO/00/75319, variants and derivatives of such VEGF receptor-based blockers are also contemplated by the invention. The sequence of the variants or derivatives may differ by a change which is one or more additions, insertions, deletions and/or substitutions of one or more nucleotides of the sequence set forth in SEQ ID NO:1. Changes to a nucleotide sequence may result in an amino acid change at the protein level, or not, as determined by the genetic code. Thus, nucleic acid according to the present invention may include a sequence different from the sequence shown in SEQ ID NO:1, yet encode a polypeptide with the same amino acid sequence as SEQ ID NO: 2. On the other hand, the encoded polypeptide may comprise an amino acid sequence which differs by one or more amino acid residues from the amino acid sequence shown in SEQ ID NO:2. Nucleic acid encoding a polypeptide which is an amino acid sequence variant or derivative of the sequence shown in SEQ ID NO:2 is further provided by the present invention. Nucleic acid encoding such a polypeptide may show at the nucleotide sequence and/or encoded amino acid level greater than about 90%, 95%, 98%, or 99% homology with the coding sequence shown in SEQ ID NO:1 and/or the amino acid sequence shown in SEQ ID NO:2. For amino acid "homology", this may be understood to be similarity (according to the established principles of amino acid similarity, e.g. as determined using the algorithm GAP (Genetics Computer Group, Madison, Wis.)) or identity. GAP uses the Needleman and Wunsch algorithm to align two complete sequences that maximizes the number of matches and minimizes the number of gaps. Generally, the default parameters are used, with a gap creation penalty=12 and gap extension penalty=4.

[0026] Individual components of the VEGF-specific fusion proteins of the invention may be constructed by molecular biological methods known to the art with the instructions provided by the instant specification. These components are selected from a first cellular receptor protein, such as, for example, VEGFR1; a second cellular receptor protein, such as, for example, VEGFR2; a multimerizing component, such as an Fc.

[0027] Specific embodiments of the VEGF-specific fusion proteins useful in the methods of the invention comprise a multimerizing component which allows the fusion proteins to associate,

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1110 of 2000

e.g., as multimers, preferably dimers. Preferably, the multimerizing component comprises an immunoglobulin derived domain. Suitable multimerizing components are sequences encoding an immunoglobulin heavy chain hinge region (Takahashi et al. 1982 Cell 29:671-679); immunoglobulin gene sequences, and portions thereof.

[0028] The nucleic acid constructs encoding the fusion proteins useful in the methods of the invention are inserted into an expression vector by methods known to the art, wherein the nucleic acid molecule is operatively linked to an expression control sequence. Host-vector systems for the production of proteins comprising an expression vector introduced into a host cell suitable for expression of the protein are known in the art. The suitable host cell may be a bacterial cell such as *E. coli*, a yeast cell, such as *Pichia pastoris,* an insect cell, such as *Spodoptera frugiperda*, or a mammalian cell, such as a COS, CHO, 293, BHK or NS0 cell.

Antisense Nucleic Acids

[0029] In one aspect of the invention, VEGF-mediated activity is blocked or inhibited by the use of VEGF antisense nucleic acids. The present invention provides the therapeutic or prophylactic use of nucleic acids comprising at least six nucleotides that are antisense to a gene or cDNA encoding VEGF or a portion thereof. As used herein, a VEGF "antisense" nucleic acid refers to a nucleic acid capable of hybridizing by virtue of some sequence complementarity to a portion of an RNA (preferably mRNA) encoding VEGF. The antisense nucleic acid may be complementary to a coding and/or noncoding region of an mRNA encoding VEGF. Such antisense nucleic acids have utility as compounds that prevent VEGF expression, and can be used in the treatment or prevention of corneal transplant rejection. The antisense nucleic acids of the invention are double-stranded or single-stranded oligonucleotides, RNA or DNA or a modification or derivative thereof, and can be directly administered to a cell or produced intracellularly by transcription of exogenous, introduced sequences.

[0028] The VEGF antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides ranging from 6 to about 50 oligonucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof and can be single-stranded or double-stranded. In addition, the antisense molecules may be polymers that are nucleic acid mimics, such as PNA, morpholino oligos, and LNA. Other types of antisence molecules include short double-stranded RNAs, known as siRNAs, and short hairpin RNAs, and long dsRNA (>50 bp but usually ≥500 bp).

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1111 of 2000

Short interfering RNAs

[0029] In another embodiment, VEGF-mediated activity is blocked by blocking VEGF expression. One method for inhibiting VEGF expression is the use of short interfering RNA (siRNA) through RNA interference (RNAi) or post-transcriptional gene silencing (PTGS) (see, for example, Ketting et al. (2001) Genes Develop. 15:2654-2659). siRNA molecules can target homologous mRNA molecules for destruction by cleaving the mRNA molecule within the region spanned by the siRNA molecule. Accordingly, siRNAs capable of targeting and cleaving homologous VEGF mRNA are useful for treating, reducing or preventing corneal transplant rejection.

Inhibitory Ribozymes

[0030] In aspect of the invention, corneal transplant rejection may be treated or prevented in a subject suffering from such disease by decreasing the level of VEGF activity by using ribozyme molecules designed to catalytically cleave gene mRNA transcripts encoding VEGF, preventing translation of target gene mRNA and, therefore, expression of the gene product.

[0031] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see, *e.g.*, U.S. Patent No. 5,093,246. While ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy mRNAs encoding VEGF, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA has the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art. The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence where after cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the gene encoding VEGF.

Generation of Antibodies to VEGF Proteins

[0032] In another aspect of the invention, the invention may be practiced with an anti-VEGF

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1112 of 2000

antibody or antibody fragment capable of binding and blocking VEGF activity. Anti-VEGF antibodies are disclosed, for example, in US Patent No. 6,121,230, herein specifically incorporated by reference. The term "antibody" as used herein refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda , alpha, gamma, delta, epsilon, and mu constant regions, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively. Within each IgG class, there are different isotypes (eg. IgG_1, IgG_2, etc.). Typically, the antigen-binding region of an antibody will be the most critical in determining specificity and affinity of binding.

[0033] Antibodies exist as intact immunoglobulins, or as a number of well-characterized fragments produced by digestion with various peptidases. For example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region. While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the terms antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv)(scFv) or those identified using phase display libraries (see, for example, McCafferty et al. (1990) Nature 348:552-554).

[0034] Methods for preparing antibodies are known to the art. See, for example, Kohler & Milstein (1975) Nature 256:495-497; Harlow & Lane (1988) Antibodies: a Laboratory Manual, Cold Spring Harbor Lab., Cold Spring Harbor, NY). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity. Techniques for the production of single chain antibodies or recombinant antibodies (US 4,946,778; US 4,816,567) can be adapted to produce antibodies used in the fusion proteins and methods of the instant invention. Also, transgenic mice, or other organisms such as other mammals, may be

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1113 of 2000

used to express human or humanized antibodies. Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens.

Antibody Screening and Selection

[0035] Screening and selection of preferred antibodies can be conducted by a variety of methods known to the art. Initial screening for the presence of monoclonal antibodies specific to a target antigen may be conducted through the use of ELISA-based methods, for example. A secondary screen is preferably conducted to identify and select a desired monoclonal antibody for use in construction of the multi-specific fusion proteins of the invention. Secondary screening may be conducted with any suitable method known to the art. One preferred method, termed "Biosensor Modification-Assisted Profiling" ("BiaMAP") is described in co-pending USSN 60/423,017 filed 01 Nov 2002, herein specifically incorporated by reference in its entirety. BiaMAP allows rapid identification of hybridoma clones producing monoclonal antibodies with desired characteristics. More specifically, monoclonal antibodies are sorted into distinct epitope-related groups based on evaluation of antibody:antigen interactions.

Treatment Population

[0036] A suitable subject for treatment by the method of the invention is a human who has received or will receive a corneal transplant. Corneal transplantation is the oldest, most successful and most commonly performed tissue transplantation, with nearly 40,000 transplantations a year alone in the US. When corneal grafts are placed into an avascular recipient bed (so-called normal-risk keratoplasty), 2-year graft survival rates approach 90% under cover of topical steroids, even without HLA-matching. This very successful outcome is attributed to corneal immune privilege, i.e. the phenomenon of suppressed corneal inflammation induced by an array of endogenous mechanisms downregulating alloimmune and inflammatory responses in the cornea and its bed. These mechanisms include the lack of both afferent lymphatic and efferent blood vessels in the normal-risk recipient cornea, lack of MHC II^+ antigen presenting cells (APCs), FASL-expression on corneal epithelium and endothelium, and the anterior chamber associated immune privilege (ACAID) directed at graft antigens etc. (Streilein et al. (1999) Transplant Proc. 31:1472-1475).

[0037] In contrast, survival rates of cornea grafts placed into vascularized, not immune-privileged recipient beds (so called high-risk keratoplasty) drop significantly to below 50% (even with local and systemic immune suppression). Pre-existing corneal stromal blood vessels have been identified as strong risk factors for immune rejection after corneal transplantation, both in

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1114 of 2000

the clinical setting as well as in the well-defined mouse model of corneal transplantation (Sano et al. (1995) Invest. Ophthalmol. Vis. Sci. 36:2176-85). Recently, in addition to blood vessels, biomicroscopically undetectable lymphatic vessels have been found in association with blood vessels in vascularized high-risk human corneas (Cursiefen et al. (2003) Cornea. 22:273-81) and it is likely that corneal lymphatic vessels enable effective access of donor and host APCs and antigenic material to regional lymph nodes where accelerated sensitisation to graft antigens occurs (Liu et al. (2002) J. Exp. Med. 195:259-68) even in the normal-risk setting (with a preoperatively avascular recipient bed), where mild corneal hemangiogenesis develops after keratoplasty. Outgrowth of new blood vessels from the limbal arcade towards the graft can be observed within the first postoperative year in about 50% of patients undergoing normal-risk keratoplasty, and in 10% of patients these new blood vessels even reach the interface or invade donor tissue (Cursiefen et al. (2001) Graefes Arch. clin. Exp. Ophthalmol. 39:514-21) at corneal suture sites, and then proceed centrally.

Methods of Administration

[0038] The invention provides methods of treatment comprising administering to a subject an effective amount of an agent of the invention. In a preferred aspect, the agent is substantially purified (*e.g.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, *e.g.,* such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0039] Various delivery systems are known and can be used to administer an active agent of the invention, *e.g.*, delivery systems suitable for topical administration, preferably topical administration directly to the eye, or subconjunctival administration, as well as other delivery systems such as those that utilize encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction are preferably topical or subconjunctival, but may be enteral or parenteral including but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, and oral routes. The active agents may be administered by any convenient route, for example by absorption through epithelial (e.g. topical administration to the eye) or mucocutaneous linings (*e.g.*, oral mucosa, intestinal mucosa, etc.) or infusion or bolus injection, and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (*e.g.* daily, weekly, monthly, etc.) or in combination or alteration with other agents. Pulmonary

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1115 of 2000

administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0040] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533). In yet another embodiment, the active agent can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer (1990) *supra*). In another embodiment, polymeric materials can be used (see Howard et al. (1989) J. Neurosurg. 71:105). In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see, for example, U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0041] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by topical administration, subconjunctival administration, local infusion during surgery, *e.g.*, by injection, by means of a catheter, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, fibers, or commercial skin substitutes.

Cellular Transfection and Gene Therapy

[0042] The present invention encompasses the use of nucleic acids encoding the VEGF-specific fusion proteins of the invention for transfection of cells *in vitro* and *in vivo*. These nucleic acids can be inserted into any of a number of well-known vectors for transfection of target cells and organisms. The nucleic acids are transfected into cells *ex vivo* and *in vivo*, through the interaction of the vector and the target cell. Reintroduction of transfected cells may be accomplished by any method known to the art, including re-implantation of encapsulated cells. The compositions are administered (e.g., by injection into a muscle) to a subject in an amount sufficient to elicit a therapeutic response. An amount adequate to accomplish this is defined as "a therapeutically effective dose or amount."

[0043] In another aspect, the invention provides a method of treating or preventing corneal transplant rejection in a human comprising transfecting a cell with a nucleic acid encoding a

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1116 of 2000

VEGF-specific fusion protein of the invention, wherein the nucleic acid comprises an inducible promoter operably linked to the nucleic acid encoding the VEGF-specific fusion protein. For gene therapy procedures in the treatment or prevention of human disease, see for example, Van Brunt (1998) Biotechnology 6:1149-1154.

Pharmaceutical Compositions

[0044] Pharmaceutical compositions useful in the practice of the method of the invention include a therapeutically effective amount of an active agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0045] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, or intramuscular administration to human beings. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0046] The active agents of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1117 of 2000

derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0047] The amount of the active agent of the invention that will be effective in the treatment or prevention of corneal transplant rejeciton can be determined by standard clinical techniques based on the present description. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each subject's circumstances. However, suitable dosage ranges for intravenous administration are generally about 50-5000 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0048] For systemic administration, a therapeutically effective dose can be estimated initially from *in vitro* assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from *in vivo* data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0049] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. One having skill in the art will be able to optimize therapeutically effective local dosages witho ut undue experimentation.

[0050] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Combination Therapies

[0051] In numerous embodiments, the VEGF blockers of the present invention may be administered in combination with one or more additional compounds or therapies or medical procedures. For example, suitable therapeutic agents for use in combination, either alternating or simultaneously, with the VEGF blockers may include topically administered immunosuppressive

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1118 of 2000

agents such as corticosteroids, dexamethasone, cyclosporin A, or anti-metabolic agents or systemically administered immunosuppressive agents such as corticosteroids, dexamethasone, cyclosporin A, FK506, or anti-metabolic agents, as well as other agents effective to treat, reduce, or prevent corneal transplant rejection (see Barker, NH, *et al.*, (2000) Clin Exp Opthal 28:357-360). Other suitable therapeutic agents for use in combination, either alternating or simultaneously, with the VEGF blockers of the subject invention may include blockers that can block other VEGF family members such as VEGF-C and VEGF-D.

Kits

[0052] The invention also provides an article of manufacturing comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention and wherein the packaging material comprises a label or package insert which indicates that the VEGF-specific fusion protein can be used for treating corneal transplant rejection.

[0053] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0054] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Inhibition of corneal lymphangiogenesis and angiogenesis after low-risk keratoplasty using VEGFR1R2-FcΔC1(a).

[0055] Mice and anesthesia. Six to 8 weeks old male C57BL/6 mice were used as donors and same-aged male BALB/c mice (Taconic, Germantown, NY) as recipients in the mouse model of normal-risk keratoplasty (Sonoda et al. (1992) Transplantation 54:694-704). For syngeneic transplantations, 6-8 weeks old male BALB/c mice were used both as donors as well as recipients. For the dose response studies, 8 weeks old male C57BL/6 mice were used. All animals were treated in accordance with the ARVO Statement for the Use of Animals in

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1119 of 2000

Ophthalmic and Vision Research. Mice were anesthetized using a mixture of ketamine and xylazine (120 mg/kg body weight and 20 mg/kg body weight respectively).

[0056] Dose response of VEGF Trap$_{R1R2}$. Five different doses of VEGF-Trap$_{R1R2}$ (SEQ ID NO:2) were tested in mice that received three interrupted intrastromal sutures (10-0 nylon, 50-μm-diameter, Sharpoint, Surgical Specialties Corporation, Reading, PA). Gentamicine and ophthalmic ointment were applied immediately after surgery. Following surgery (day 0), mice received a single subcutaneous injection of VEGF Trap$_{R1R2}$ (25 mg/kg, 12.5 mg/kg, 6.25 mg/kg, 2.5 mg/kg or 0.5 mg) or human Fc (12.5 mg/kg; control). Corneas were harvested on day 9 after suture placement, following an intravenous administration of an endothelial-specific fluorescein-conjugated lectin (*Lycopersicon esculentum*, Vector Laboratories, Burlingame, CA). The isolated corneas were flat-mounted on glass slides, and images of lectin-labeled vessels were captured using a Spot RT Digital camera (Diagnostic Instrument, Inc. Sterling Heights, MI) attached to a Nikon Microphot-FXA microscope (Nikon Inc. Garden City, NY). Scion Image 1.62c (Scion Corporation, Frederick, MD) was used to quantify the extent of corneal neovascularization.

[0057] Corneal transplantation in mice. Orthotopic corneal allografting in the mouse model of normal-risk keratoplasty was performed as described previously (Sonoda et al. (1992) *supra*). Donor corneas were excised by trephination using a 2.0 mm bore and cut with a curved vannas scissor. Until grafting, corneal tissue was placed in chilled phosphate-buffered saline. Recipients were anesthetized and the graft bed was prepared by trephining a 1.5 mm site in the central cornea of the right eye and discarding the excised cornea. The donor cornea was immediately applied to the bed and secured in place with 8 interrupted sutures (11-0 nylon, 70 μm diameter needles, Arosurgical, Newport Beach, CA). Antibiotic ointment (Oxymycin, Pharmafair, Hauppauge, NY) was placed on the corneal surface and the eyelids sutured with 8-0 suture (Sharpoint, Reading, PA). Recipients of grafts in which bleeding developed in the immediate postoperative period were discarded from further evaluation. All grafted eyes were examined after 72 hours, and grafts with technical difficulties (hyphema, cataract, infection, loss of anterior chamber) were excluded from further consideration. Tarsorraphy and corneal sutures were removed after 7 days and grafts were then examined at least twice a week until week 8 post transplantation by slit-lamp microscopy and scored for opacity. The survival experiment was performed twice and comprised 10 and 12 mice per experiment in both groups, respectively. Clinical scores of corneal grafts for opacity were as follows: 0= clear; +1=minimal, superficial (nonstromal) opacity; pupil margin and iris vessels readily visible through the cornea; +2= minimal, deep (stroma) opacity; pupil margins and iris vessels visible; +3= moderate stromal opacity; only pupil margin visible; +4= intense stromal opacity; only a portion of pupil margin

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1120 of 2000

visible; +5= maximum stromal opacity; anterior chamber not visible. Grafts with opacity scores of +2 or greater after 2 weeks were considered to have been rejected. Syngeneic transplantations were performed and evaluated in a similar manner.

[0058] Immunohistochemistry and morphometry of angiogenesis and lymphangiogenesis in the cornea. Briefly, corneal flat mounts were rinsed in PBS, fixed in acetone, rinsed in PBS, blocked in 2% bovine serum albumin, stained with FITC-conjugated CD31/PECAM-1 overnight (Santa Cruz Biotechnology, Santa Cruz, CA; 1:100), washed, blocked, stained with LYVE-1 (1:500; a lymphatic endothelium specific hyaluronic acid receptor (Cursiefen et al. (2002) Invest. Ophthalmol. Vis. Sci. 43:2127-35) washed, blocked, and stained with Cy3 (1:100; Jackson ImunoResearch Laboratories, West Grove, PA) and analyzed using a Zeiss Axiophot microscope. Digital pictures of the flat mounts were taken using Spot Image Analysis system. Then the area covered by $CD31^{+++}$/LYVE-1^{-} blood vessels and $CD31^{+}$/LYVE-1^{+++} lymph vessels was measured morphometrically on these flat-mounts using NIH Image software. The total corneal area was outlined using the innermost vessel of the limbal arcade as the border. The total area of blood versus lymphatic neovascularization was then normalized to the total corneal area and the percentage of the cornea covered by each vessel type calculated.

[0059] Neutralization of VEGF-A using VEGF $Trap_{R1R2}$. The VEGF $trap_{R1R2}$ (Regeneron Pharmaceuticals Inc, Tarrytown, NY (Holash et al. (2002) Proc. Natl. Acad. Sci. USA 99:11393-8, herein specifically incorporated by reference in its entirety) was used in the transplant survival experiment at a concentration of 12.5 mg/kg intraperitoneally (i.p.) at time of surgery (CHO hVEGFR1 [Ig domain 2] R2 [Ig domain 3]-Fc), and 3, 7, and 14 days after surgery. Human Fc-fragment given i.p. at same concentration and times was used in the control mice (sCHO h Fc).

[0060] Statistical analysis. Statistical significance was analyzed by Mann-Whitney's test. Differences were considered significant at $P < 0.05$. Each experiment was performed at least twice with similar results. Graphs were drawn using Graph Pad Prism, Version 3.02.

[0061] Results. Dose response of angiogenesis inhibition by VEGF $Trap_{R1R2}$. VEGF-$Trap_{R1R2}$ at doses of either 25 mg/kg or 12.5 mg/kg completely inhibited suture-induced inflammatory corneal neovascularization. In contrast, doses of 6.25mg/kg and 2.5mg/kg produced ~50% and ~20% inhibition of corneal neovascularization, respectively, while the lowest dose tested, 0.5 mg/kg, had a negligible effect (<5% inhibition). Therefore, for subsequent experiments a dose of 12.5 mg/kg VEGF $Trap_{R1R2}$ was chosen.

[0062] Rapid and parallel onset of hemangiogenesis and lymphangiogenesis *after* normal-risk allogeneic corneal transplantation. To determine whether the mild and temporary hemangiogenesis occurring *after* normal-risk keratoplasty is accompanied by lymphatic vessel outgrowth from the limbus into the normally alymphatic cornea, we studied the time course of

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1121 of 2000

ingrowth of both vessel types at days 0, 3, 7, 14, 21, and 28 *after* allogeneic keratoplasty (only accepted grafts). Immediately *after* surgery, blood and lymphatic vessels were not detectable either in the host or in donor tissue using biomicroscopy and immunohistochemistry on corneal flat mounts. But, at day 3 after allografting, both methods revealed new blood vessels growing into the cornea already 1/3 to halfway towards the graft interface. By day 7 these vessels had usually reached the donor tissue, but they rarely invaded the donor tissue itself. Analyzing flatmounts stained with LYVE-1 as a lymphatic vessel specific marker showed that $CD31^{+++}$/LYVE-1^{-} blood vessels were regularly accompanied by LYVE-1^{+++}/$CD31^{+}$ lymphatic vessels. Both vessel types reached the interface simultaneously at day 7. Thereafter, coincident with suture removal, both vessel types started to regress (if no immune rejection occurred; data not shown).

[0063] No difference in postkeratoplasty hem- and lymphangiogenesis between syngeneic and allogeneic corneal transplantation. To determine whether the simultaneous induction of hem- and lymphangiogenesis *after* normal-risk keratoplasty is primarily an effect of the surgical trauma, suturing and wound healing processes or secondary to early immunological rejection reactions, we compared speed and extent of both hem- and lymphangiogenesis occurring *after* keratoplasty between allogeneic (C57BL/6 into BALB/c) and syngeneic grafts (BALB/c into BALB/c) at day 3, 7, 14, 21, 28 after transplantation. In both groups, blood and lymphatic vessels grew out after keratoplasty and by day 3 reached about 1/3 to _ of the limbus-interface distance. At day 7 after syngeneic and allogeneic grafting both vessel types had reached the interface, before they started to regress thereafter. Furthermore, there was no significant difference in the hem- and lymphvascularized area, comparing syngeneic and allogeneic grafts at 3 days (allogeneic: hemvascularized area [HA] 25.2±4.1% and lymphvascularized area [LA] 22.2±9.4% versus syngeneic HA: 23±2.7% and LA 19.4±7.2%) and 7 days (allogeneic HA: 53.8±11.2% and LA: 37.9±6.2% versus syngeneic HA: 55.9±8.2% and LA: 38±22.7%) after surgery (n=8 mice per group per timepoint).

[0064] Neutralization of VEGF-A after normal-risk keratoplasty inhibits postoperative hemangiogenesis and lymphangiogenesis. Mice received either intraperitoneal injections of VEGF $Trap_{R1R2}$ (12.5 mg/kg) at surgery and 3 days later, or in the controls the Fc-protein in the same dosage. At day 3 and 7 after surgery, the extent of hem- and lymphangiogenesis was compared between these two groups (n=6 mice per group per timepoint). At day 3 and day 7 after surgery, the hemvascularized area was significantly smaller in trap-treated mice (day 3: 15.8±4.0%; day 7: 25.2±13.3%) compared to mice just receiving the Fc-fragment (day 3: 25.8±4.4%; day 7: 48.3±12.8%; $p<0.0001$). This was also true for the lymphvascularized area

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1122 of 2000

comparing Trap- (9.5±9.4%) and Fc-treated mice on day 3 (21.5±9.3%; $p<0.0001$). At day 7, the lymphvascularized area was smaller, but not significantly different in the Trap-group (28.7±20.3%) compared to the Fc-group (51.5±23.8%; $p=0.06$). In contrast to results obtained in corneal injury models neither hem- or lymphangiogenesis were completely inhibited by the VEGF $Trap_{R1R2}$ following corneal transplantation. However, the number of lymphatic vessels reaching the graft-host interface (10.6±0.6 versus 1.3±1.5 vessels) and the number of hours where the interface was filled with draining lymphatic vessels were much larger in the Fc-treated compared to the Trap-treated group (3±2 versus 0.2±0.3 hours; not significant due to small sample size) at day 7. This might indicate that lymphavascularized area per se is less decisive for host sensitisation than the contact area with donor tissue.

[0065] Partial inhibition of early postoperative hem- and lymphangiogenesis by trapping VEGF-A after normal-risk surgery improves long-term graft survival.

Since hem- and lymphangiogenesis occurring *after* normal-risk keratoplasty peaked around day 7, and regressed thereafter, and since both vascular processes could be significantly inhibited by early postoperative neutralization of VEGF-A, we determined whether inhibition of postkeratoplasty hem- and lymphangiogenesis during this interval improves graft survival. The long-term survival of C57BL/6 grafts placed into avascular BALB/c recipient beds was compared between mice receiving an i.p. injection of 12.5 mg/kg VEGF $Trap_{R1R2}$, or Fc-fragment alone, at surgery and 3, 7, and 14 days later. Trapping of VEGF-A postoperatively caused a significantly improved long-term graft survival at 8 weeks (78%), compared to grafts in eyes of Fc-treated controls (40%; $p=0.044$; $n=22$ in both groups).

[0066] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1123 of 2000

Claims

We claim,

1. Use of an first agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity in the preparation of a medicament for treating or preventing corneal transplant rejection in a mammalian subject.

2. The use of claim 1, wherein the agent capable of blocking, inhibiting, or ameliorating VEGF-mediated activity is a VEGF antagonist.

3. The use of claim 2, wherein the VEGF antagonist is a polypeptide, an antibody, a small molecule, or a nucleic acid.

4. The use of claim 3, wherein the VEGF antagonist includes a VEGF trap selected from the group consisting of acetylated Flt-1(1-3)-Fc, Flt-1(1-$3_{R->N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt-1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3D3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a).

5. The use of claim 4, wherein the VEGF trap is VEGFR1R2-FcΔC1(a).

6. The use of claim 3, wherein the VEGF antagonist is a nucleic acid selected from the group consisting of aptamer, an siRNA, or an antisense molecule.

7. The use of claim 1, wherein administration is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, oral, subconjunctival, or topical. Administration may also include a second agent, such as an immunosuppressive agent.

8. The use of claim 1, further comprising administering a second agent.

9. The use of claim 8, wherein the second agent is an immunosuppressive agent.

10. The use of claim 1, wherein the mammalian subject is a human.

11. The use of claim 10, wherein the human subject has received a corneal transplant.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1124 of 2000

12. A method of reducing the incidence of corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that the incidence of corneal transplant rejection is reduced.

13. A method of treating corneal transplant rejection in a subject in need thereof, comprising administering to the subject an agent capable of blocking, inhibiting, or ameliorating vascular endothelial growth factor (VEGF)-mediated activity, such that corneal transplant rejection is treated.

14. A pharmaceutical composition for prevention or treatment of corneal transplant rejection, comprising a vascular endothelial growth factor (VEGF) antagonist, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, in the form of a liquid, gel, ointment, salve, or ophthalmic solution.

16. An article of manufacturing comprising:

(a) packaging material; and

(b) a pharmaceutical agent contained within the packaging material;

wherein the pharmaceutical agent comprises at least one VEGF-specific fusion protein of the invention and wherein the packaging material comprises a label or package insert which indicatess that the VEGF-specific fusion protein can be used to treat or prevent corneal transplant rejection in a mammalian subject.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1125 of 2000

SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.
The Schepens Eye Research Institute

<120> Method of Treating Corneal Transplant Rejection

<130> REG 713B-WO

<140> To be Assigned
<141> 2004-04-23

<160> 2

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 1377
<212> DNA
<213> homo sapiens

<400> 1
atggtcagct actgggacac cggggtcctg ctgtgcgcgc tgctcagctg tctgcttctc 60
acaggatcta gttccggaag tgataccggt agacctttcg tagagatgta cagtgaaatc 120
cccgaaatta tacacatgac tgaaggaagg gagctcgtca ttccctgccg ggttacgtca 180
cctaacatca ctgttacttt aaaaaagttt ccacttgaca ctttgatccc tgatggaaaa 240
cgcataatct gggacagtag aaagggcttc atcatatcaa atgcaacgta caaagaaata 300
gggcttctga cctgtgaagc aacagtcaat gggcatttgt ataagacaaa ctatctcaca 360
catcgacaaa ccaatacaat catagatgtg gttctgagtc cgtctcatgg aattgaacta 420
tctgttggag aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt 480
gacttcaact gggaataccc ttcttcgaag catcagcata agaaacttgt aaaccgagac 540
ctaaaaaccc agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt 600
gtaacccgga gtgaccaagg attgtacacc tgtgcagcat ccagtgggct gatgaccaag 660
aagaacagca catttgtcag ggtccatgaa aaggacaaaa ctcacacatg cccaccgtgc 720
ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 780
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 840
gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 900
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 960
caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 1020
gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 1080
accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1140
aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 1200
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1260
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1320
gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga 1377

<210> 2
<211> 458
<212> PRT
<213> homo sapiens

<400> 2
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
1 5 10 15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1126 of 2000

```
                20                  25                  30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
            35                  40                  45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
        50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
```


Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1127 of 2000

FREE
ARVO Annual Meeting Abstract | May 2007

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

M. S. Benz; Q. D. Nguyen; K. Chu; A. Cahn; I. Grimes; A. Ingerman; J. M. Cedarbaum

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science May 2007, Vol.48, 4549. doi:

Abstract

Purpose:: To determine the safety, tolerability, and biological effect of repeated intravitreal (ITV) injection of VEGF Trap in patients with neovascular age-related macular degeneration (AMD).

Methods:: Five groups of patients with neovascular AMD were randomized in a balanced ratio to receive a series of ITV injections of one of 3 dose levels of VEGF Trap (0.5, 2 or 4 mg) into the study eye at 4- or 12-week intervals over a 12-week period. Measures of bioactivity included changes from baseline in best-corrected ETDRS visual acuity (BCVA), foveal thickness, and macular volume determined by optical coherence tomography, as well as total lesion and CNV area determined by fluorescein angiography. Dosing was continued beyond week 12 using a criteria-based schedule.

Results:: The study is currently ongoing and treatment assignments remain masked. No ocular serious adverse events, no identifiable intraocular inflammation or serious drug-related systemic adverse events have been reported to date.

Conclusions:: Repeated intravitreal VEGF Trap administration according to the dosing regimens employed in this study appears to be safe and well tolerated. Safety and bioeffect data will be updated at time of presentation.

Clinical Trial:: www.clinicaltrials.gov NCT00320788

Keywords: age-related macular degeneration • retina • clinical (human) or epidemiologic studies: outcomes/complications

© 2007, The Association for Research in Vision and Ophthalmology, Inc., all rights reserved. Permission to republish any abstract or part of an abstract in any form must be obtained in writing from the ARVO Office prior to publication.

FREE

ARVO Annual Meeting Abstract | May 2007

Results of a Phase I Study of Intravitreal VEGF Trap in Subjects With Diabetic Macular Edema: The CLEAR-IT DME Study

D. V. Do; Q. D. Nguyen; D. J. Browning; J. A. Haller; K. Chu; J. Buskey; I. Grimes; A. Ingerman; J. Cederbaum; P. A. Campochiaro

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science May 2007, Vol.48, 1430. doi:

Abstract

Purpose:: To determine the safety, tolerability, and bioactivity of a single dose (4.0mg) of intravitreal VEGF Trap in patients with diabetic macular edema (DME).

Methods:: Five patients with DME, foveal thickness ≥ 250µm measured by optical coherence tomography (OCT) and ETDRS best-corrected visual acuity (BCVA) of ≤ 20/40 and ≥ 20/320 were administered a single intravitreal injection of 4 mg VEGF Trap at day 0. Safety assessments included eye examinations, vital signs, and laboratory tests. Measures of bioactivity included changes from baseline in BCVA, centerpoint retinal thickness (CRT), and leakage on fluorescein angiography. Subjects were monitored for 6 weeks following VEGF Trap administration.

Results:: Mean patient age was 65.2 years (range=56-75); 4 were Type 2 diabetics. Mean duration of diabetes prior to treatment was 26 years. All had received prior treatment for DME. No severe ocular or serious systemic adverse events related to study drug were noted. Mean baseline BCVA was 69 letters and mean baseline CRT was 407µm. Four patients had improvements in BCVA, ranging from 6 to 10 letters at 4 weeks post-injection. The mean decrease in centerpoint retinal thickness was 115µm at 4 weeks.

Conclusions:: A single intravitreal dose of VEGF Trap was well-tolerated and led to a reduction in CRT and an improvement in BCVA. Although the number of subjects is small, preliminary evidence for bioactivity of VEGF Trap in patients with DME was detected.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1130 of 2000

Additional studies are being planned to identify the potential therapeutic role of intravitreal VEGF Trap in DME.

Clinical Trial:: www.clinicaltrials.gov NCT 00320814

Keywords: diabetic retinopathy • macula/fovea • clinical (human) or epidemiologic studies: treatment/prevention assessment/controlled clinical trials

© 2007, The Association for Research in Vision and Ophthalmology, Inc., all rights reserved. Permission to republish any abstract or part of an abstract in any form must be obtained in writing from the ARVO Office prior to publication.

FREE

ARVO Annual Meeting Abstract | April 2009

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

D. V. Do; CLEAR-IT 2 Investigators

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science April 2009, Vol.50, 1887. doi:

Abstract

Purpose: : To examine the effects of VEGF Trap-Eye on patient-reported vision-specific Quality of Life (QoL) using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) in CLEAR-IT 2: a Phase 2 randomized trial in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Methods: : CLEAR-IT 2 was a randomized, double masked, multi-center Phase 2 trial. Patients received intravitreal injections of VEGF Trap-Eye 0.5 or 2.0 mg monthly or 0.5, 2.0, or 4.0 mg quarterly for 12 weeks, followed by PRN dosing based on results of OCT and clinical examination out to 52 weeks. The NEI-VFQ 25 was administered to patients at baseline, week 12, and week 52. QoL was assessed at 52 weeks by change in mean score from baseline. The NEI-VFQ 25 subscales are scored from 0-100; a positive difference represents improved functioning or reduced dependency. Pre-specified subscales included near activities, distance activities, and vision related dependency.

Results: : The mean overall change from baseline to 52 weeks in the total score of the NEI-VFQ 25 for all treatment groups combined (n=145) was +4.5. For all groups combined patients had mean changes of +5.7 for near activities, +3.4 for distance activities and +5.8 for vision related dependency. Patients receiving the 2.0 mg dose monthly for the first 12 weeks (2mg q4 group, n=28) had a change from baseline of +4.5 in the total score, +6.8 for near activities, +4.6 for distance activities, and +11.6 for vision related dependency at 52 weeks.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1132 of 2000

Conclusions: : Patients treated with multiple doses of VEGF Trap-Eye over a 52 week period had overall improvements in the patient-reported vision-specific QoL (total scores as well as subscales) as assessed by the NEI-VFQ 25. As a clinically meaningful change is often considered to be ±5 points, the most notable improvements were seen in the 2mg q4 group for near activities and for vision related dependency.

Clinical Trial: : www.clinicaltrials.gov NCT00320788

Keywords: age-related macular degeneration • quality of life • clinical (human) or epidemiologic studies: treatment/prevention assessment/controlled clinical trials

© 2009, The Association for Research in Vision and Ophthalmology, Inc., all rights reserved. Permission to republish any abstract or part of an abstract in any form must be obtained in writing from the ARVO Office prior to publication.

FREE

ARVO Annual Meeting Abstract | April 2011

VEGF Trap-Eye In CRVO: Primary Endpoint Results Of The Phase 3 COPERNICUS Study

Julia A. Haller; David S. Boyer; Jeffrey S. Heier; David M. Brown; Lloyd Clark; Robert Vitti

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science April 2011, Vol.52, 6643. doi:

Abstract

Purpose: : VEGF Trap-Eye is an intravitreally administered fusion protein that is designed to bind the pro-angiogenic factors VEGF-A and placental growth factor with higher affinity than their natural receptors. This study evaluated the efficacy and safety of VEGF Trap-Eye in patients with macular edema secondary to central retinal vein occlusion (CRVO) after 24 weeks of treatment.

Methods: : In this randomized, double-masked, controlled Phase 3 study, 114 patients received 6 monthly injections of 2 mg VEGF Trap-Eye and 73 patients received control sham injections. Visual acuity was measured as a score based on the total number of Early Treatment of Diabetic Retinopathy Study (ETDRS) letters read correctly. The primary endpoint was the proportion of patients who gained at least 15 ETDRS letters from baseline at 24 weeks. A key secondary endpoint was the mean change in best-corrected visual acuity from baseline at 24 weeks.

Results: : The primary endpoint was met in this study: 56.1% of patients receiving 2 mg VEGF Trap-Eye monthly gained at least 15 letters of vision from baseline, compared with 12.3% of patients receiving sham injections ($p<0.0001$). Patients receiving VEGF Trap-Eye gained a mean of 17.3 letters of vision compared with a mean loss of 4.0 letters with sham injection ($p<0.001$). The most common adverse events were those typically associated with intravitreal injections and/or the underlying disease. The proportions of patients who experienced serious ocular adverse events were 3.5% in the VEGF Trap-Eye group and 13.5% in the sham group. The incidence of non-ocular serious adverse events was generally well balanced between the treatment and sham groups.

Conclusions: : Dosing monthly with 2 mg VEGF Trap-Eye in patients with macular edema secondary to CRVO resulted in a statistically significant improvement in visual acuity compared with control sham treatment. VEGF Trap-Eye was generally well tolerated and had a generally favorable safety profile.

Clinical Trial: : http://www.clinicaltrials.gov NCT00943072

Keywords: vascular endothelial growth factor • visual acuity • vascular occlusion/vascular occlusive disease

© 2011, The Association for Research in Vision and Ophthalmology, Inc., all rights reserved. Permission to republish any abstract or part of an abstract in any form must be obtained in writing from the ARVO Office prior to publication.

FREE
ARVO Annual Meeting Abstract | April 2009

CLEAR-IT 2: Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap Eye in Patients With Neovascular Age-Related Macular Degeneration: Predictive Factors for Visual Acuity Outcome at One Year

J. S. Heier; CLEAR-IT 2 Investigators

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science April 2009, Vol.50, 1255. doi:

Abstract

Purpose: : To evaluate potential predictive factors for visual acuity outcomes in patients with neovascular AMD after repeated intravitreal injections of VEGF Trap-Eye over one year.

Methods: : CLEAR-IT 2 was a double-masked, multi-center Phase 2 trial in AMD patients randomized to receive VEGF Trap-Eye 0.5 or 2.0 mg monthly or 0.5, 2.0, or 4.0 mg quarterly (at baseline and week 12) with monthly reassessment and PRN dosing to 1 year. Subgroups of patients were identified based on age, baseline best-corrected visual acuity (BCVA), baseline lesion size, and previous treatment for neovascular AMD.

Results: : Data through one year for all dose groups combined (n=157) demonstrated significant improvement in BCVA (mean increase of 5.3 letters, $p<0.0001$.) Analyses of the subgroups identified above generated the following results for all treatment groups combined: Patients that were ≤75 years old (n=53) gained an average of 8.26 (±13.55) letters as opposed to those >75 years old (n=104) who gained 3.73 (±13.31) letters ($p=0.046$). Those with a BCVA ≤54 letters at baseline (n=65) gained an average of 7.54 (±15.44) letters as opposed to those with a BCVA at baseline > 54 letters (n=92) who gained

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1136 of 2000

3.65 (±11.8) letters (p=0.076). Those who began the study with a lesion size ≤4DA (n=124) gained an average of 5.52 (±13.63) letters, while those who began the study with lesions >4DA gained 4.27 (±13.23) letters (p=0.63). Patients who were treatment naïve at the start of the study (n=137) gained an average of 4.8 (±13.7) letters, while those who received previous treatment (n=20) gained an average of 8.4 (±12.09) letters (p=0.27).

Conclusions: : In this study, ≤75 years of age at baseline predicted greater visual acuity gains following multiple treatments of VEGF Trap-Eye. In addition, worse baseline visual acuity was suggestive of better visual acuity outcomes. Baseline lesion size and previous treatment status did not significantly affect treatment responses.

Clinical Trial: : www.clinicaltrials.gov NCT00320788

Keywords: age-related macular degeneration • choroid: neovascularization • vascular endothelial growth factor

© 2009, The Association for Research in Vision and Ophthalmology, Inc., all rights reserved. Permission to republish any abstract or part of an abstract in any form must be obtained in writing from the ARVO Office prior to publication.

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

Jeffrey S. Heier, MD,[1] David Boyer, MD,[2] Quan Dong Nguyen, MD, MSc,[3] Dennis Marcus, MD,[4] Daniel B. Roth, MD,[5] George Yancopoulos, MD, PhD,[6] Neil Stahl, PhD,[6] Avner Ingerman, MD, MSc,[6] Robert Vitti, MD, MBA,[6] Alyson J. Berliner, MD, PhD,[6] Ke Yang, PhD,[6] David M. Brown, MD,[7] for the CLEAR-IT 2 Investigators

Objective: To evaluate anatomic outcomes and vision, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with vascular endothelial growth factor (VEGF) Trap-Eye for neovascular (wet) age-related macular degeneration (AMD).

Design: Multicenter, randomized, double-masked trial.

Participants: We included 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD.

Methods: Patients were randomly assigned to 1 of 5 intravitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1–12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their assigned dose (0.5, 2, or 4 mg).

Main Outcome Measures: Change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in best-corrected visual acuity (BCVA), proportion of patients with 15-letter loss or gain, time to first PRN injection, reinjection frequency, and safety at week 52.

Results: The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (−130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm^2 at 48 weeks. After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; $P<0.0001$). The most robust improvements and consistent maintenance of visual acuity generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first reinjection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well tolerated, with few ocular or systemic adverse events.

Conclusions: PRN dosing with VEGF Trap-Eye at weeks 16-52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of reinjections. Repeated dosing with VEGF Trap-Eye was well tolerated over 52 weeks of treatment.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:1098–1106 *© 2011 by the American Academy of Ophthalmology.*

Vascular endothelial growth factor (VEGF) is a critical regulator of normal ocular vasculogenesis and angiogenesis during development.[1–3] Vascular endothelial growth factor also plays a central role in the abnormal growth of new blood vessels in the retina, as well as in vascular leakage that causes retinal edema and thickening, both of which characterize diseases such as neovascular (wet) age-related macular degeneration (AMD) and diabetic retinopathy that lead to loss of retinal function.[3–6] Of the various members of the VEGF gene family, VEGF-A and placental growth factor (PlGF) are the factors implicated in pathologic angiogenesis and the pathogenesis of AMD (Invest Ophthalmol Vis Sci 50 [Suppl]: 2943,2009).[7–9]

An improved understanding of the pivotal role of VEGF in pathologic angiogenesis has resulted in the development and use of intravitreal anti-VEGF therapies in wet AMD and other eye diseases that have an angiogenesis-based etiology.[10–12] Pegaptanib, an oligoribonucleotide aptamer,

 © 2011 by the American Academy of Ophthalmology
Published by Elsevier Inc.
ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2011.03.020

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1138 of 2000

and ranibizumab, a humanized monoclonal antibody fragment, are anti-VEGF therapies currently available for intravitreal treatment of neovascular AMD. In pivotal trials, pegaptanib mainly slowed loss of visual acuity, whereas ranibizumab improved visual function in a substantial proportion of patients.[13–16] Bevacizumab is an off-label intravitreal anti-VEGF therapy that has also been shown in less rigorous studies to improve visual function.[17–20]

The beneficial results with ranibizumab were obtained with a fixed-dosing regimen requiring an injection of ranibizumab 0.5 or 0.3 mg every month for 2 years in the pivotal phase 3 studies, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR).[13,15] Several studies were undertaken to examine different dosing regimens for ranibizumab. In a large, randomized study in which patients were initially treated with a 3-month loading regimen of ranibizumab and then dosed at regular quarterly intervals, the initial gains after the loading regimen were not maintained at a year.[21] A 40-patient uncontrolled, open-label, single-site, Prospective Optical Coherence Tomography Imaging of Patients Treated with intra-Ocular ranibizumab (PrONTO) trial evaluated an as-needed (PRN) dosing regimen (based on monthly evaluation of changes in retinal thickness and edema using optical coherence tomography [OCT]) after 3 consecutive monthly injections. Visual acuity outcomes at 12 and 24 months were comparable with those observed in the pivotal phase 3 studies and were attained with fewer intravitreal injections.[22,23] However, in a larger randomized study, the gains in visual acuity after an initial 3-month loading regimen of ranibizumab were not maintained with subsequent protocol-defined retreatment.[24]

Vascular endothelial growth factor Trap-Eye (VEGF Trap-Eye) is a potent, specific VEGF antagonist that binds and inactivates circulating VEGF and VEGF in the extravascular space. It was developed specifically as an ultrapurified, isoosmotic solution for ophthalmic use.[25] Consisting of extracellular portions of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G, VEGF Trap-Eye binds both VEGF-A or PlGF and forms an inert 1:1 complex with the growth factor dimers.[24,25] Thus, VEGF Trap-Eye has broader anti-VEGF activity compared with pegaptanib, which binds only the VEGF-A_{165} isoform,[26] and ranibizumab, which neutralizes all active isoforms of VEGF-A, but not PlGF.[27] Because VEGF Trap-Eye contains only human sequences, its potential for immunogenicity is low. A key differentiating feature of VEGF Trap-Eye is its picomolar affinity for VEGF ligands, which is substantially higher than that of the natural receptors or anti-VEGF monoclonal antibodies.[25,28,29] The clinical relevance of the higher binding affinity of VEGF Trap-Eye remains unknown, but it is thought that it might lead to more persistent VEGF blockade and a theoretically longer dosing interval between injections to maintain visual acuity relative to currently available anti-VEGF treatments.[30]

The clinical efficacy of VEGF-Trap Eye was initially demonstrated in the CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1), a 6-week phase 1 sequential cohort, single-ascending-dose (0.05 to 4 mg) study of intravitreal VEGF Trap-Eye in patients with neovascular AMD.[31] The efficacy and safety of repeated dosing with VEGF Trap-Eye were subsequently examined in the phase 2 CLEAR-IT 2 study, which consisted of an initial 12-week fixed dosing period with 1 of 5 monthly or quarterly regimens of VEGF Trap-Eye, followed by PRN dosing from weeks 16 to 52. Detailed results to 16 weeks for the fixed-dosing phase, including the primary endpoint at week 12, are presented in the accompanying article (Brown et al., in this issue, pp 1089-97). At 12 weeks, treatment with VEGF Trap-Eye resulted in a significant reduction in central retinal/lesion thickness (CR/LT) of -119 μm and a significant improvement in mean BCVA of 5.7 letters for all groups combined, and gains of >8 letters in the monthly dosing groups. The finding that improvements in visual acuity and retinal thickness were greater in the monthly dosing groups than in the quarterly dosing groups at week 12, support the need for an initial intensive monthly loading dose phase. Patients were treated with a PRN dosing regimen through week 52 to explore whether the high affinity of VEGF Trap-Eye for VEGF-A and PlGF could translate into the maintenance of initial visual acuity gains through 1 year with less frequent intravitreal injections. Results of the continued dosing phase of the CLEAR-IT 2 study are reported herein.

Materials and Methods

Study Design

The primary objectives of the study were to assess the effect of intravitreal VEGF Trap-Eye on CR/LT and to assess the ocular and systemic safety and tolerability of repeated doses of VEGF Trap-Eye in patients with choroidal neovascularization (CNV) associated with wet AMD. A key secondary objective was to assess the effect of VEGF Trap-Eye on BCVA.

This study was a double-masked, prospective, randomized, dose- and interval-ranging study in which 5 groups of approximately 30 patients each were assigned to a fixed-dose of intravitreal VEGF Trap-Eye in the study eye during the first 12 weeks of dosing, followed by PRN dosing from weeks 16 to 52 (Fig 1, available online at http://aaojournals.org). The VEGF Trap-Eye regimens were 0.5 mg or 2 mg at 4-week intervals (0.5q4 or 2q4 on day 1 and at weeks 4, 8, and 12 for a total of 4 treatments) or 0.5, 2, or 4 mg every 12 weeks (0.5q12, 2q12, or 4q12 on day 1 and week 12 for a total of 2 treatments). During the PRN dosing phase beginning at week 16, patients received the same dose of VEGF Trap-Eye (0.5, 2, or 4 mg) as received during the fixed-dosing phase (Fig 2).

The study protocol was approved by the ethics committee at every institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. The study was compliant with the rules and regulations under the Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent to participate in the study. The CLEAR-IT 2 study is registered with ClinicalTrials.gov (NCT00320788).

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1139 of 2000

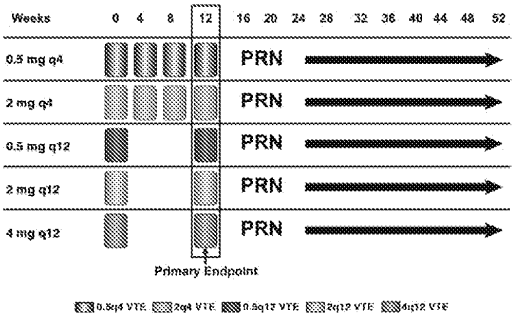


Figure 2. Study schedule. During the 12-week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses; those in the quarterly dosing groups received 0.5, 2, or 4 mg of VEGF Trap-Eye every 12 weeks on day 0 and at week 12 for a total of 2 doses. Beginning at week 16 and continuing to week 52, patients were assessed every 4 weeks and, if needed, were retreated with the same dose of VEGF Trap-Eye as in the fixed dosing phase. The primary study endpoint was assessed at week 12. q = every; PRN = as-needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Patient Population

The study enrolled patients >50 years old who had a diagnosis of subfoveal CNV secondary to wet AMD and central retinal thickness ≥300 μm, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA of 73 to 34 letters, loss of ≥5 ETDRS letters in BCVA over the preceding 6 months for previously treated patients with minimally classic or occult lesions, linear diameter of lesion ≤5400 μm by fluorescein angiography (FA), subretinal hemorrhage sparing the fovea and comprising ≤50% of total lesion, area of scar ≤25% of total lesion, and sufficient clarity of ocular media to allow retinal photography.

Key exclusion criteria were history of vitreous hemorrhage in preceding 4 weeks; aphakia or pseudophakia with absence of a posterior capsule (unless as a result of a yttrium aluminum garnet capsulotomy); significant subfoveal atrophy or scarring; presence of other causes of CNV in either eye; previous treatments for AMD in the study eye within 12 weeks for photodynamic therapy, 8 weeks for pegaptanib sodium, or 24 weeks for intravitreal or juxtascleral steroids; no other treatments for AMD (thermal laser, surgery, or intraocular/systemic anti-VEGF therapy) were allowed; any retinal vascular disease other than CNV in either eye; active ocular inflammation or infection; history of trabeculectomy or pars plana vitrectomy; history of myocardial infarction, stroke, transient ischemic attack, symptomatic peripheral vascular disease, or treatment for congestive heart failure within the last 6 months; and other conditions or laboratory abnormalities that might interfere with patient participation in the study.

Retreatment Criteria

During the fixed-dosing phase, 1 eye was designated as the study eye and all evaluations were conducted on that eye as described previously (Brown et al, in this issue, pp 1089-97). Beginning at week 16, patients were evaluated every 4 weeks to determine the need for continued dosing. After week 16, the study eye was reinjected with VEGF Trap-Eye if any of the following changes were observed by the evaluating practitioner: An increase in CR/LT ≥100 μm as measured by OCT; a loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; persistent fluid as indicated by OCT; new-onset classic neovascularization; new or persistent leak on FA; or new macular hemorrhage.

Endpoints and Assessments

Assessments were performed at scheduled clinic visits on days 1 and 7, at week 4, and every 4 weeks thereafter to week 52. At each visit, patients underwent a full ophthalmologic examination, including visual acuity testing, indirect ophthalmoscopy and slit lamp examination, intraocular pressure (IOP) measurement, and OCT. Fundus photography and FA were performed at baseline and at weeks 4, 12, 24, 36, and 48.

The primary efficacy endpoint was reduction of CR/LT from baseline to 12 weeks, at the end of the fixed-dosing phase. The variables assessed during the PRN dosing phase included change from baseline in CR/LT and mean change from baseline in CNV size determined by FA at 48 weeks, the last mandatory FA in the study; BCVA at 52 weeks; proportions of patients with avoidance of moderate vision loss (loss of <15 letters); stabilization or improvement in visual acuity (gain of ≥0 letters); and significant vision gain (gain of ≥15 letters) at 52 weeks; time to first reinjection after week 12; and mean number of injections over the PRN period.

The CR/LT was determined from Stratus OCT (Version 4.0 or higher; CarlZeiss, Jena, Germany) scans read at a masked independent central reading center (Digital OCT Reading Center, Cleveland, OH). The CR/LT was defined as the distance between the inner limiting membrane and posterior border of retinal pigment epithelial/choriocapillaris complex including any subretinal fluid and thickness of any observable choroidal neovascular membrane or scar tissue in central 1 mm of posterior pole scan.

Changes in the size of the total lesion and the CNV component were evaluated with FA. The CNV size was defined as the area of visible CNV (classic or occult) with angiographic evidence of late leakage or pooling of dye. Angiographic images were transmitted to the masked reading center for review (Digital Angiography Reading Center, New York, NY). At least 1 designated photographer was certified by the Reading Center before enrollment of the first patient at each site.

Certified examiners assessed BCVA by using the ETDRS protocol at 4 m. Examiners were masked to treatment assignment, and performed no other study assessments.

Safety assessments included IOP (measured preinjection and approximately 30 minutes postinjection), ophthalmologic examinations for ocular toxicity, adverse events (AEs), serious AEs (SAEs), clinical laboratory tests, and vital signs.

Statistical Analysis

Efficacy assessments were made on the full analysis set, which included all patients who received study treatment and had a baseline and ≥1 postbaseline assessment. Safety assessments were performed on all patients who received study treatment.

The primary analysis was a paired comparison t test of the change in CR/LT from baseline to week 12 for all groups combined. If this was significant, an analysis of covariance was done on the 5 individual groups. A similar analysis was done for all continuous measures at all time points. Missing values were imputed using the last-observation-carried-forward method for continuous measures. The durability of the effect was assessed by evaluating all of the endpoints out to week 52. All of the analyses shown below were done using the same methods at week 12 and week 52 (week 48 for FA parameters).

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1140 of 2000

Table 2. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated Patients (n = 157)
Age, y (mean [range])	78.3 (53–94)
Gender (%M:%F)	38:62
Disease duration, months (mean [range])	3.9 (0–67)
Previous treatment	20 (12.7%)
Lesion size (mean ± SD) in disc area	3.11 ± 2.12
Lesion type (n [%])	
Predominantly classic	60 (38.2)
Minimally classic	37 (23.6)
Occult lesions	60 (38.2)
Disease status (mean [range])	
Central retinal/lesion thickness (μm)	456 (186–1316)
Foveal thickness (μm)	327 (116–1081)
Best-corrected visual acuity (ETDRS letters)	56 (27–83)

ETDRS = Early Treatment of Diabetic Retinopathy Study; F = Female; M = Male; SD = standard deviation.

Results

Patient Disposition

Of 159 patients who were randomized, 157 were treated and 134 (85.4%) completed 52 weeks in the study (Table 1 available online at http://aaojournal.org). For the 23 patients (14.6%) who were withdrawn before completion of 52 weeks, 6 (3.8%) withdrawals were at the request of the patient.

Baseline Characteristics

The study population was representative of the AMD population in the United States. Patients ranged in age from 53 to 94 years (mean, 78.3) and the majority were women (62%; Table 2). The mean time from diagnosis was 3.9 months (range, 0–67), and 12.7% of patients had received previous treatment. The distribution of CNV lesions was 38.2% predominantly classic, 23.6% minimally classic, and 38.2% occult with no classic. The treatment groups were well-balanced overall for baseline disease severity, but mean CR/LT and mean foveal thickness were somewhat higher in the 4 mg q12wk group (Table 3).

Change in Central Retinal/Lesion Thickness

The primary efficacy endpoint of the study was mean change in CR/LT at week 12. In all treatment groups combined, the significant decrease from baseline in CR/LT observed at week 12 (−119 μm) was maintained to week 52 (−130 μm; $P<0.0001$) after 40 weeks of PRN dosing with VEGF Trap-Eye (Fig 3A). The decrease in CR/LT was also maintained in all individual dosing groups after PRN dosing and was significant compared with baseline values. The greatest decreases in CR/LT at week 52 versus baseline occurred in the 4 mg q12wk group (−161 μm; $P = 0.0002$) and the 2 mg q4wk group (−143 μm; $P<0.0001$; Fig 3B).

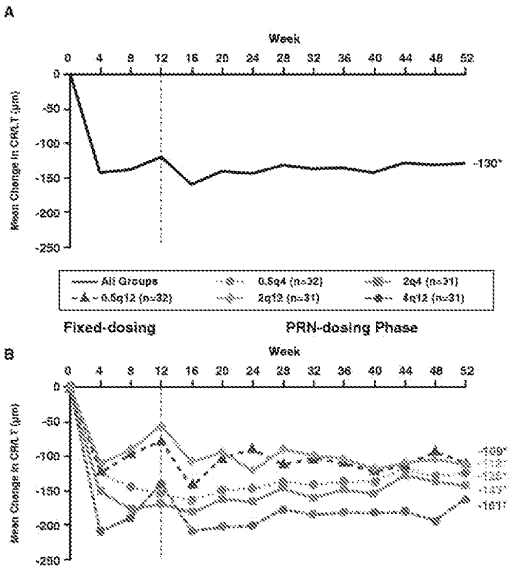


Figure 3. Mean change in central retinal/lesion (CR/LT) thickness in (**A**) all treatment groups combined and (**B**) individual treatment groups. The CR/LT was measured with optical coherence tomography. Change in CR/LT from baseline at 12 weeks was the primary study endpoint. In the combined treatment group, a significant (*$P<0.0001$) decrease in CR/LT at week 12 was maintained to week 52 (−130 μm). The decrease in CR/LT in individual treatment groups was maintained between weeks 12 and 52 with PRN dosing was significant (*$P<0.0001$; †$P = 0.0002$) compared with baseline values. The last-observation-carried-forward method was used to impute missing data. CR/LT = central retina/lesion thickness; PRN = as-needed; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Change in Angiographic Measures

Fluorescein angiography (FA) was performed at baseline and at weeks 4, 12, 24, 36, and 48. In all groups combined and in each treatment group, there were no significant changes in total lesion

Table 3. Baseline Disease Status by Treatment Group

Mean (Range)	0.5q4 (n = 32)	2q4 (n = 31)	0.5q12 (n = 32)	2q12 (n = 31)	4q12 (n = 31)	All Groups (n = 157)
CR/LT (μm)	434 (282–710)	453 (232–960)	442 (186–762)	447 (265–948)	507 (240–1316)	456 (186–1316)
Foveal thickness (μm)	329 (212–509)	307 (171–524)	319 (116–559)	334 (186–762)	360 (177–1081)	327* (116–1081)
BCVA (ETDRS letters)	54 (27–76)	58 (32–83)	56 (30–72)	57 (32–72)	53 (28–80)	56 (27–83)

BCVA = best-corrected visual acuity; CR/LT = central retinal/lesion thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; q = every.
*In all groups (n = 157), 25 patients at week 52 showed foveal thickness measurements of <150 μm.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1141 of 2000

size from baseline to week 12 and week 48 (data not shown). The decrease in total lesion size for the 2 mg q4wk group at week 12 (-0.75 mm^2; -0.30 disc area [DA]) and week 48 (-1.75 mm^2; -0.69 DA; $P<0.04$) achieved significance.

The area of CNV (defined as classic and/or occult CNV demonstrating angiographic evidence of late leakage or pooling of dye) was also measured. In all treatment groups combined, PRN treatment with VEGF Trap-Eye resulted in a consistent decrease in the CNV size versus baseline at weeks 12 and 48, with a decrease of -2.21 mm^2 (-0.87 DA) at week 48 ($P<0.001$; Fig 4A, available online at http://aaojournal.org). All treatment groups other than the 0.5 mg q12wk group experienced a decrease in active CNV size at 48 weeks (-1.42 to -3.41 mm^2; -0.56 to -1.34 DA), with the greatest reduction in the 2 mg q4wk group (-3.41 mm^2, -1.34 DA; $P<0.001$; Fig 4B).

Change in Visual Acuity

The significant improvement from baseline in BCVA that was noted at 12 weeks was maintained through the PRN dosing phase to week 52. The combining of all treatment groups showed a mean gain of 5.7 letters at week 12 and 5.3 letters at week 52 ($P<0.0001$ vs baseline; Fig 5A). The greatest improvement in BCVA occurred in the 2 mg q4wk treatment group, with a mean increase of 8.3 letters at week 12 and of 9.0 letters at week 52 ($P<0.0001$ vs baseline; Fig 5B). Visual acuity improvements compared with baseline were also maintained in all other treatment groups at week 52.

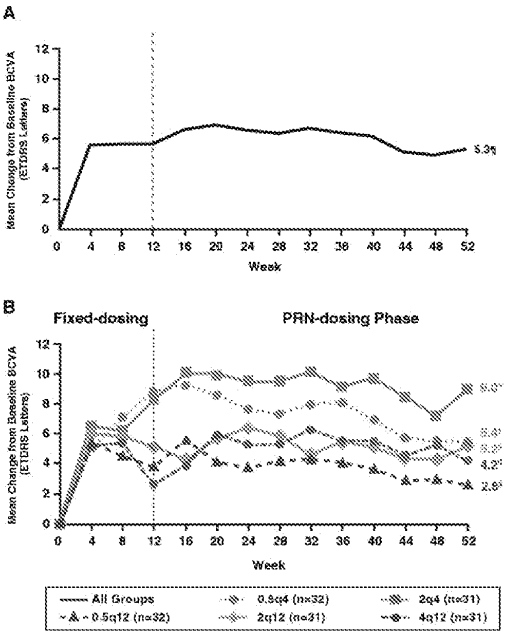


Figure 5. Mean change in best-corrected visual acuity (BCVA) in (A) all treatment groups combined and (B) individual treatment groups. The BCVA was assessed with the Early Treatment of Diabetic Retinopathy Study protocol at 4 m. Significant improvements from baseline in BCVA were noted in all treatment groups combined at week 12 (5.7 letters) and were maintained to week 52 (5.3 letters; ¶$P<0.0001$). The 2 mg q4wk group showed the greatest gain in BCVA at 12 weeks, which was maintained to 52 weeks (9.0 letters; *$P<0.0001$; †$P = 0.085$; ‡$P = 0.0412$; §$P = 0.0154$; and ‖$P = 0.344$ for individual groups versus baseline). The last-observation-carried-forward method was used to impute missing data. ETDRS = Early Treatment of Diabetic Retinopathy Study; PRN = as-needed.

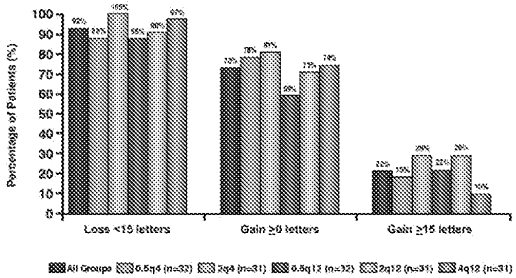


Figure 6. Visual acuity changes at week 52. The proportions of patients who avoided moderate vision loss (≥15 letters), had an improvement in visual acuity (gain of ≥0 letters), or had a significant vision gain (≥15 letters) in the treatment groups combined and individual dosing groups at week 52 are shown. In the treatment groups combined, only 8% of patients experienced moderate loss of vision, whereas 22% showed a significant gain in vision of ≥15 letters at week 52 after 40 weeks of as-needed (PRN) dosing. The last-observation-carried-forward method was used to impute missing data. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Frequency of Patients with Visual Acuity Changes

In all treatment groups combined, moderate loss of vision (loss of ≥15 letters) was avoided in 98% of patients at week 12 and 92% at week 52 after treatment with VEGF Trap-Eye. In the individual treatment groups, 88% to 100% of patients avoided moderate loss of vision at week 52 (Fig 6). Overall, 12 patients experienced moderate vision loss at week 52, including 4 in the 0.5 mg q4wk group, 4 in the 0.5 mg q12wk group, 3 in the 2 mg q12wk group, and 1 in the 4 mg q12wk group. None of the patients in the 2 mg q4wk group experienced moderate vision loss.

Stabilization or improvement in visual acuity (gain of ≥0 letters) occurred in 74.5% of patients in all treatment groups combined at week 12 and in 73% of patients at week 52. In the individual treatment groups, the proportion of patients experiencing stable or improved visual acuity ranged between 59% and 81%, with the highest proportion in the 2 mg q4wk group. Overall, these proportions remained steady from week 12 to week 52.

The frequency of patients in all treatment groups combined with a significant gain in vision (≥15 letters) was 18.5% at week 12 and 22% at week 52. Groups treated with 2 mg, either monthly or quarterly, had the highest frequency of patients with significant visual gain (26% and 16%, respectively, at week 12, and 29% in each group at week 52).

The proportion of patients with ≤20/200 vision in all treatment groups combined was 11.5% at baseline and remained stable at 10.8% at week 52. The proportion of patients with ≥20/40 vision increased from baseline (15%) to week 52 (41%) for all groups combined, with the 0.5mg q4wk and 2mg q4wk groups increasing from 13% and 16% to 47% and 45%, respectively (Fig 7, available online at http://aaojournal.org).

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1142 of 2000

Table 4. Retreatment Outcomes with VEGF Trap-Eye

Treatment Regimen	Mean No. of Injections over PRN Phase (Weeks 12–52)	Mean No. of Days to First Injection over PRN Phase (Weeks 12–52)	Median No. of Days to First Injection over PRN Phase (Months 3–12)
0.5 mg q4	2.52	102	85
2 mg q4	1.55	160	150
0.5 mg q12	1.84	133	86
2 mg q12	2.48	113	86
4 mg q12	1.7	138	111
All groups	2.01	129	110

PRN = as-needed.

Reinjection Outcomes

Beginning at week 16, patients were evaluated monthly for the need for reinjection. Over the 40-week PRN dosing phase, the mean number of reinjections received for all groups combined was 2.01, ranging from 1.55 injections in the 2 mg q4wk group to 2.52 in the 0.5 mg q4wk group (Table 4). During the PRN dosing phase, 29 patients (19%) did not receive any injections of VEGF Trap-Eye, 45% received 1 to 2 injections, and only 5% of patients received ≥5 injections (Fig 8). The most common reason for retreatment was the presence of persistent fluid on OCT examination (63%); in 26% of patients who needed retreatment, a new or persistent leak was noted on FA, and 25% of patients had a loss of BCVA of ≥5 ETDRS letters with recurrent fluid on OCT (Table 5 available online at http://aaojournal.org).

The average time from the last mandatory injection at week 12 to the first PRN injection was 129 days for all treatment groups combined. The longest initial treatment-free interval was in the 2 mg q4wk group (160 days; Table 4). This calculation accounts for the 29 patients who were not reinjected by assigning them a reinjection time at 52 weeks and is therefore an underestimate of the true mean. Kaplan–Meier analysis of the time to first reinjection showed a median time to reinjection for all groups combined of 110 days. The longest median time to reinjection was 150 days in the 2 mg q4wk group (Fig 9, available online at http://aaojournal.org; Table 4).

Safety

The types and frequencies of ocular AEs occurring in the study eye were consistent with AEs previously reported with intravitreal anti-VEGF treatment and were generally related to the intravitreal injection procedure (Table 6). In all treatment groups combined, conjunctival hemorrhage (38.2%) was the most frequently reported AE in the study eye. Most ocular AEs in the study eye were mild (58%), with 4 events considered severe (conjunctival hemorrhage, reduced visual acuity, uveitis, and increased IOP). Seven patients (4.5%) had an increase in IOP in the study eye that was considered related to study treatment, but the increased IOP was not considered an SAE and did not lead to withdrawal of patients from the study. Most ocular events that occurred in the fellow eye were mild (41.4%) or moderate (12.7%); the most frequently reported AE in the fellow eye was vitreous detachment (8.9%).

The number of patients with systemic AEs was similar among treatment groups. The most commonly reported systemic AEs were urinary tract infection (10.2%), bronchitis (9.6%) and upper respiratory tract infection (9.6%). A total of 58 systemic SAEs were reported in 35 patients, but none of the events was deemed to be related to study treatment. Two deaths occurred during the study, one from pancreatic carcinoma and the other from preexisting pulmonary hypertension. Four ocular SAEs were reported: Culture-negative endophthalmitis/uveitis (0.5 mg q4wk group) and decreased visual acuity (0.5 mg q12wk group) in the study eye and increased IOP (4 mg q12wk group) and retinal detachment (0.5 mg q12wk group) in the fellow eye. Stroke was reported in 1 patient in the 0.5 mg q4wk group who had a history of stroke. No cases of vascular death were reported in this study.

Adverse events resulted in withdrawal of 7 patients from the

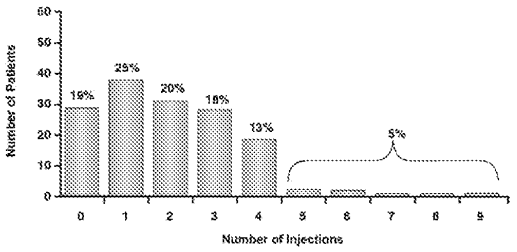


Figure 8. Number of injections after loading phase. Numbers of patients receiving 0 to 9 injections of VEGF Trap-Eye during the as-needed dosing period are shown. Overall, 19% of patients required no retreatment, 45% received 1 or 2 retreatments, and only 5% required 5 to 9 retreatments. VEGF = vascular endothelial growth factor.

Table 6. Ocular Adverse Events in the Study Eye (Frequency ≥5% in All Groups Combined*)

Adverse Event	Number (n)	Percent (%)
Conjunctival hemorrhage	60	38.2
Increased IOP (transient postinjection)	29	18.5
Refraction disorder	26	16.6
Retinal hemorrhage	22	14.0
Visual acuity reduced (patient reported)	21	13.4
Vitreous detachment	18	11.5
Eye pain	15	9.6
Vitreous floaters	14	8.9
Detachment of retinal pigment epithelium	12	7.6
Retinal edema	10	6.4
Visual disturbance	8	5.1
Blepharitis	8	5.1
Subretinal fibrosis	8	5.1

IOP = intraocular pressure.
*Patients receiving treatment with VEGF Trap-Eye (n = 157).

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1143 of 2000

study: Three ocular (retinal edema and retinal hemorrhage in the study eye and increased IOP in the fellow eye) and 4 systemic (non-Hodgkin's lymphoma, hip fracture, colon cancer, and bronchitis). There were no differences in frequency of AEs or SAEs between the treatment groups.

Discussion

Among patients with neovascular AMD, PRN dosing with VEGF Trap-Eye maintained efficacy established during a 12-week monthly or quarterly fixed-dosing phase for an additional 40 weeks. For all groups combined, a clinically significant improvement in visual acuity achieved at 12 weeks (5.7-letter gain) was maintained to 52 weeks (5.3-letter gain), accompanied by a decrease in CR/LT (−119 μm at week 12 and −130 μm at week 52). Among patients in all treatment groups combined, 22% experienced a gain of ≥15 letters and only 8% of patients had a loss of ≥15 letters at the end of the study period. These improvements were achieved with an average of only 2 additional injections of VEGF Trap-Eye over the 40-week PRN phase; notably, 44% of patients required either no retreatment or only 1 reinjection, suggesting a long duration of effect in these patients. Repeated intravitreal dosing of VEGF Trap-Eye was generally safe and well tolerated. The overall safety profile was similar to that previously reported with other intravitreal anti-VEGF agents.

Anti-VEGF treatment offers the hope of improved vision and is now the standard of care for neovascular AMD; however, the need for frequent monitoring and treatment places a significant burden on both the patient and the clinician. In addition, the injection procedure itself has associated risks, which, although rare, may be increased with repeated injections. Hence, a less frequent dosing regimen that is maximally effective in preserving or improving visual acuity is a desirable goal of anti-VEGF treatment for AMD.

With VEGF Trap-Eye, the improvements in visual acuity achieved with a 12-week fixed dosing schedule were maintained to week 52 with an average of 2 injections over the 9-month period after fixed dosing. In the 2 mg q4wk group, ≥50% of patients remained injection free for 150 days after week 12. The best visual acuity outcomes to date with ranibizumab have been achieved with 3 consecutive monthly injections, followed by continuous monthly injections.[13,15,32] Less frequent dosing with ranibizumab using both fixed and PRN schedules has been investigated. In the 2-year Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Safety and Efficacy of Ranibizumab (PIER), study a regimen of 3 consecutive monthly injections followed by fixed quarterly injections provided vision gains at 3 months that were comparable with those in the pivotal clinical studies; however, these gains declined with quarterly dosing and returned to baseline levels at 12 months.[21] Results of a phase 3b study designed to evaluate the long-term effect of ranibizumab in patients with all subtypes of neovascular AMD (The Safety Assessment of Intravitreal Lucentis for AMD [SAILOR]) suggested that treating patients with ranibizumab on a PRN basis was less effective than monthly dosing, although retreatment criteria and follow-up schedules in this study were less well-defined and investigator determined.[33] In the open-label HORIZON extension study, patients received PRN dosing with ranibizumab after 2 years of monthly dosing, resulting in a decline in visual acuity gain at years 3 and 4 (Invest Ophthalmol Vis Sci 50 [Suppl]:3093, 2009).

The 52-week results of the CLEAR-IT 2 study suggest that the efficacy of VEGF Trap-Eye, established with an initial fixed-dosing regimen, is maintained with PRN dosing and that VEGF Trap-Eye has an extended duration of action. The average time from last mandatory injection to first PRN injection for all groups combined was >4 months and for the 2 mg q4wk group, >5 months. The high binding affinity of VEGF Trap-Eye, its presumed long intravitreal half-life, and activity against multiple VEGF family members, including PlGF, may contribute to more sustained and comprehensive VEGF suppression than may be achieved with currently used anti-VEGF agents. Based on its binding affinity and estimated intravitreal half-life in humans, a mathematical model has predicted that, after intravitreal injection, VEGF Trap-Eye would maintain biological activity for 10 to 12 weeks, whereas ranibizumab would maintain such activity for 30 days, supporting the concept of less frequent dosing with VEGF Trap-Eye.[30]

By the end of the fixed-dosing phase at week 12, VEGF Trap-Eye showed a significant improvement in visual acuity from baseline, and this efficacy was maintained to week 52. However, patients randomized to monthly injections during the fixed dosing phase had a trend toward improved visual acuity outcomes at 52 weeks compared with those randomized to quarterly injections. This difference was apparent at 12 weeks and was maintained throughout the 40-week PRN phase, despite the fact that all patients were treated as often as necessary during this phase. Therefore, initial sequential monthly loading doses seem to provide better control of neovascular leakage and lead to superior gains in visual acuity that can be subsequently maintained with less frequent dosing.

Ongoing phase 3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in wet Age-Related Macular Degeneration, VIEW-1 and VIEW-2) are evaluating VEGF Trap-Eye doses of 0.5 and 2 mg every 4 weeks and 2 mg every 8 weeks after 3 initial monthly doses, compared with ranibizumab 0.5 mg every 4 weeks. The rationale for the 2 mg q8wk dose was based on an observation from the fixed-dosing phase of CLEAR-IT 2: At 8 weeks, the improvement in BCVA after a single 2-mg dose was similar to that obtained with 2 mg dosed monthly to 8 weeks and that the effect in visual acuity gain for the single dose groups began to wane by week 12.

After the first year of treatment on the above schedule, patients in the VIEW-1 and -2 studies will be evaluated monthly and treated on a PRN basis. To prevent undertreatment, the PRN dosing schedule during the second year of the study does not allow any patient to remain untreated for >12 weeks. Although many patients in the CLEAR-IT 2 study did maintain initial visual acuity gains for >12 weeks, the design of the phase 3 program is meant to optimize visual improvements for all patients by using this capped

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1144 of 2000

PRN dosing schedule. These studies should provide further information on the duration and extent of the clinical benefit of VEGF Trap-Eye.

In conclusion, PRN dosing of VEGF Trap-Eye after 12 weeks of monthly or quarterly fixed dosing maintained clinically and statistically significant improvements in vision and retinal thickness to week 52 in patients with neovascular AMD, with a low frequency of reinjection. VEGF Trap-Eye was generally well-tolerated, with a safety profile similar to that reported with other intravitreally administered anti-VEGF agents.

Acknowledgment. Technical writing and editorial assistance was provided by Meher Dustoor, PhD.

References

1. Maharaj AS, D'Amore PA. Roles for VEGF in the adult. Microvasc Res 2007;74:100–13.
2. Tammela T, Enholm B, Alitalo K, Paavonen K. The biology of vascular endothelial growth factors. Cardiovasc Res 2005; 65:550–63.
3. Penn J, Madan A, Caldwell R, et al. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008;27: 331–71.
4. Grisanti S, Tatar O. The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res 2008;27:372–90.
5. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338–46.
6. Aiello L, Avery R, Arrigg P, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480–7.
7. Rakic J, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci 2003;44:3186–93.
8. Olsson A, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling-in control of vascular function. Nat Rev Mol Cell Biol 2006;7:359–71.
9. Boyer DS, Antoszyk AN, Awh CC, et al, MARINA Study Group. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:246–52.
10. Waisbourd M, Loewenstein A, Goldstein M, Leibovitch I. Targeting vascular endothelial growth factor: a promising strategy for treating age-related macular degeneration. Drugs Aging 2007;24:643–62.
11. van Wijngaarden P, Qureshi S. Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice. Clin Exp Optom 2008;91:427–37.
12. Ip M, Scott I, Brown G, et al. Anti–vascular endothelial growth factor pharmacotherapy for age-related macular degeneration: a report by the American Academy of Ophthalmology. Ophthalmology 2008;115:1837–46.
13. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
14. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology 2008;115:116–26.
15. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
16. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–16.
17. Gunther J, Altaweel M. Bevacizumab (Avastin) for the treatment of ocular disease. Surv Ophthalmol 2009;54:372–400.
18. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007; 143:679–80.
19. Park JE, Chen HH, Winer J, et al. Placenta growth factor: potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. J Biol Chem 1994;269:25646–54.
20. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–72.
21. Regillo CD, Brown DM, Abraham P, et al, PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
22. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566–83.
23. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009;148:43–58.
24. Rudge J, Holash J, Hylton D, et al. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A 2007;104:18363–70.
25. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393–8.
26. Lee JH, Canny MD, De Erkenez A, et al. A therapeutic aptamer inhibits angiogenesis by specifically targeting the heparin binding domain of VEGF165. Proc Natl Acad Sci U S A 2005;102:18902–7.
27. Lowe J, Araujo J, Yang J, et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. Exp Eye Res 2007;85:425–30.
28. Konner J, Dupont J. Use of soluble recombinant decoy receptor vascular endothelial growth factor trap (VEGF Trap) to inhibit vascular endothelial growth factor activity. Clin Colorectal Cancer 2004;4(suppl):S81–5.
29. Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs 2009;18:1573–80.
30. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–8.
31. Nguyen QD, Shah SM, Browning DJ, et al. A phase I study of intravitreal vascular endothelial growth factor Trap-Eye in patients with neovascular age-related macular degeneration. Ophthalmology 2009;116:2141–8.
32. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2–13.
33. Boyer DS, Heier JS, Brown DM, et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009; 116:1731–9.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1145 of 2000

Footnotes and Financial Disclosures

Originally received: October 29, 2010.
Final revision: March 14, 2011.
Accepted: March 15, 2011. Manuscript no. 2010-1500.

[1] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[2] Retina Vitreous Association Medical Group, Beverly Hills, California.

[3] The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

[4] Southeast Retina Center, Augusta, Georgia.

[5] Retina-Vitreous Center, New Brunswick, New Jersey.

[6] Regeneron Pharmaceuticals, Inc., Tarrytown, New York.

[7] Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

Presented at: The Retina Society, October, 2009; American Academy of Ophthalmology Annual Meeting, October, 2009; International Symposium on Ocular Pharmacology and Therapeutics, December 2009; Association for Research in Vision and Ophthalmology Annual Meeting, April, 2010.

Financial Disclosure(s):
The authors have made the following disclosures:

Jeffrey S. Heier – Regeneron (C,S), Alcon (C), Genentech (C), Glaxosmithkline (C), Paloma (C), Neovista (C), Oraya (C).

David Boyer – Alcon (C,L), Genentech (C,L), Regeneron (C), Novartis (C), Pfizer (C), Eyetech (C), Allergan (C,L).

Quan Dong Nguyen – Genetech (S), Regeneron (S), Novartis (S), Pfizer (S), Lux Biosciences (S), Macu Sight (S), Bausch & Lomb (C).

Dennis Marcus – Genentech (C,S), Regeneron (S), Allergan (S), Neovista (S), Pfizer (S), Ophthotech (S), Alimaera (S).

Daniel B. Roth – Regeneron (C), Allergan (C), Notal Vision (C).

George Yancopoulos – Regeneron (E,O).

Neil Stahl – Regeneron Pharmaceuticals (E).

Avner Ingerman – Regeneron Pharmaceuticals (E).

Robert Vitti – Regeneron Pharmaceuticals (E).

Alyson J. Berliner – Regeneron Pharmaceuticals (E).

Ke Yang – Regeneron Pharmaceuticals (E, O).

David M. Brown – Thrombogenics(S), Molecular Partners (C,S), Schering Plough (S), Paloma (C,S), Alimaera (S), Ophthotech (S).

Supported by Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG. The sponsors participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and the preparation, review and approval of the manuscript.

Correspondence:
David M. Brown, MD, Retina Consultants of Houston, The Methodist Hospital, 6560 Fannin, Suite 750, Houston, TX 77030. E-mail: dmbmd@houstonretina.com.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1146 of 2000

initial work were those that were underrepresented or excluded. Indeed, eyes at the extreme of axial length and keratometry, high astigmatism, postrefractive patients, and eyes with previous surgery (e.g., penetrating keratoplasty) are notorious for difficulty in estimation of the postoperative IOL position. Analysis of these groups may demonstrate significant improvement to a very difficult problem.

Another question, and the most difficult to address, is how to address the postoperative standard of care for our patients. We believe that there is enough evidence at this time to suggest evaluating the postoperative refraction of the first eye in most patients. Refractive stability after cataract surgery occurs within a few weeks, and thus, waiting for the second eye should be considered. Our current practice is to wait at least 3 to 4 weeks between surgeries, which allows for analysis of the refractive result among other postoperative factors. Bilateral simultaneous surgery, which has been advocated by some investigators, would obviously preclude a patient from these potential advantages. Finally, we thank the authors of these 2 large retrospective studies, which will further enhance our collective outcomes as we strive for postoperative refractive perfection.

References

1. Preferred Practice Patterns. American Academy of Ophthalmology. Cataract in the Adult Eye, 2006.
2. Norrby S. Sources of error in intraocular lens power calculation. J Cataract Refract Surg 2008;34:368–76.
3. Aristiodemou P, Cartwright NE, Sparrow JM, Johnston RL. Intraocular lens formula constant optimization and partial coherence interferometry biometry: refractive outcomes in 8108 eyes after cataract surgery. J Cataract Refract Surg 2011; 37:50–62.
4. Covert DJ, Henry CR, Koenig SB. Intraocular lens power selection in the second eye of patients undergoing bilateral, sequential cataract extraction. Ophthalmology 2010;117: 49–54.
5. Olsen T. Use of fellow eye data in the calculation of intraocular lens power for the second eye. Ophthalmology 2011;118: 1710–5.
6. Aristodemou P, Cartwright NE, Sparrow JM, Johnston RL. First eye prediction error improves second eye refractive outcome: results in 2129 patients after bilateral sequential cataract surgery. Ophthalmology 2011;118:1701–9.
7. User group for Laser Interference Biometry. Optimized IOL Constants for the Zeiss IOL Master. http://augenklinil.uniwuerzburg.de/ulib/c1.htm. Accessed May 17, 2011.

Erratum

With apologies from the authors, the legend for Figure 5 in "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;1098-106) contained errors in the order of some of the *P* values. Below is the corrected legend with changes in boldface.

Figure 5. Mean change in best-corrected visual acuity (BCVA) in (**A**) all treatment groups combined and (**B**) individual treatment groups. The BCVA was assessed with the Early Treatment of Diabetic Retinopathy Study protocol at 4 m. Significant improvements from baseline in BCVA were noted in all treatment groups combined at week 12 (5.7 letters) and were maintained to week 52 (5.3 letters; $^{\P}P < 0.0001$). The 2 mg q4wk group showed the greatest gain in BCVA at 12 weeks, which was maintained to 52 weeks (9.0 letters; $^{*}P < 0.0001$; $^{\dagger}P = 0.085$; $^{\ddagger}\mathbf{P = 0.344}$; $^{\S}\mathbf{P = 0.0412}$; **and** $^{\|}\mathbf{P = 0.0154}$ for individual groups versus baseline). The last-observation-carried-forward method was used to impute missing data. ETDRS = Early Treatment of Diabetic Retinopathy Study; PRN = as-needed.

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1147 of 2000

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	◉	◉	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: June 8, 2011 (v8)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: June 2011

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	June 8, 2011
Last Update Posted:	June 10, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C. Part A is a dose escalation. Part B was terminated early. The (one) subject who received Macugen is not discussed in this website. Part C had

subjects receive one of two doses of VEGF Trap (0.15 mg or 4.0 mg).

This is the first study in which human subjects received intravitreal injections of VEGF Trap in a study eye.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	◉	◉	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: January 25, 2011 (v7)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: January 2011

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 25, 2011
Last Update Posted:	January 26, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C. Part A is a dose escalation. Part B was terminated early. The (one) subject who received Macugen is not discussed in this website. Part C had

subjects receive one of two doses of VEGF Trap (0.15 mg or 4.0 mg).

This is the first study in which human subjects received intravitreal injections of VEGF Trap in a study eye.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	◉	◉	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: January 26, 2010 (v6)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: January 2010

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 26, 2010
Last Update Posted:	January 27, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C. Part A is a dose escalation. Part B was terminated early. The (one) subject who received Macugen is not discussed in this website. Part C had

subjects receive one of two doses of VEGF Trap (0.15 mg or 4.0 mg).

This is the first study in which human subjects received intravitreal injections of VEGF Trap in a study eye.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	◉	◉	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: April 29, 2009 (v5)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: April 2009

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	April 29, 2009
Last Update Posted:	April 30, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C. Part A is a dose escalation. Part B was terminated early. The (one) subject who received Macugen is not discussed in this website. Part C had

subjects receive one of two doses of VEGF Trap (0.15 mg or 4.0 mg).

This is the first study in which human subjects received intravitreal injections of VEGF Trap in a study eye.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	◉	◉	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: January 23, 2009 (v4)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: January 2009

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 23, 2009
Last Update Posted:	January 27, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 1

Interventional Study Model: Parallel Assignment

Number of Arms: 3

Masking: None (Open Label)

Allocation: Randomized

Enrollment: 51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Sham Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability of Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Neovascular Age-Related Macular Degeneration (AMD)

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification

Version	A	B	Submitted Date	Changes
3	◉	◉	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: July 25, 2007 (v3)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability of Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Neovascular Age-Related Macular Degeneration (AMD)

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	July 2007
Overall Status:	Active, not recruiting
Study Start:	June 2005
Primary Completion:	
Study Completion:	
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	July 25, 2007
Last Update Posted:	July 27, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This study consists of three parts, Part A, Part B and Part C.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 1

Interventional Study Model:

Number of Arms:

Masking: (masked roles unspecified)

Allocation: N/A

Enrollment: 96

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
4. Extent of CNV leakage
5. Anti-VEGF Trap antibodies in the systemic circulation
6. Plasma levels of VEGF Trap

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director

Locations: **United States, Arizona**

Tuscon, Arizona, United States, 85704

United States, California

Loma Linda, California, United States, 92354

United States, Illinois

Chicago, Illinois, United States, 60637

United States, Maryland

Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte, North Carolina, United States, 28120

United States, Ohio

Cleveland, Ohio, United States, 44195

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Wisconsin

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability of Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Neovascular Age-Related Macular Degeneration (AMD)

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	◉	◉	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification

Version	A	B	Submitted Date	Changes
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: October 3, 2006 (v2)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability of Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Neovascular Age-Related Macular Degeneration (AMD)

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	April 2006
Overall Status:	Recruiting
Study Start:	June 2005
Primary Completion:	
Study Completion:	
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	October 3, 2006
Last Update Posted:	October 4, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This study consists of three parts, Part A, Part B and Part C.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 1

Interventional Study Model:

Number of Arms:

Masking: (masked roles unspecified)

Allocation: N/A

Enrollment: 96

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
4. Extent of CNV leakage
5. Anti-VEGF Trap antibodies in the systemic circulation
6. Plasma levels of VEGF Trap

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Central Contact: Regeneron

Email: VEGF.Trap@regeneron.com

Locations: **United States, Arizona**

[Recruiting]

Tuscon, Arizona, United States, 85704

United States, California

[Recruiting]

Loma Linda, California, United States, 92354

United States, Illinois

[Recruiting]

Chicago, Illinois, United States, 60637

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21287

United States, North Carolina

[Recruiting]

Charlotte, North Carolina, United States, 28120

United States, Ohio

[Recruiting]

Cleveland, Ohio, United States, 44195

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	◉	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification

Version	A	B	Submitted Date	Changes
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	○	○	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: April 28, 2006 (v1)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	April 2006
Overall Status:	Recruiting
Study Start:	June 2005
Primary Completion:	
Study Completion:	June 2006
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	April 28, 2006
Last Update Posted:	May 3, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C.

Conditions

Conditions: Neovascular Age-Related Macular Degeneration

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 1

Interventional Study Model:

Number of Arms:

Masking: (masked roles unspecified)

Allocation: N/A

Enrollment: 96

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on: excess central retinal/lesion thickness, best-corrected ETDRS visual acuity, extent of CNV leakage, anti-VEGF Trap antibodies in the systemic circulation, plasma levels of VEGF Trap

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by OCT.
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Central Contact: Regeneron
Email: VEGF.Trap@regeneron.com

Locations: **United States, Arizona**

[Recruiting]
Tuscon, Arizona, United States, 85704

United States, California

[Recruiting]
Loma Linda, California, United States, 92354

United States, Illinois

[Recruiting]
Chicago, Illinois, United States, 60637

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21287

United States, North Carolina

[Recruiting]

Charlotte, North Carolina, United States, 28120

United States, Ohio

[Recruiting]

Cleveland, Ohio, United States, 44195

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1217 of 2000

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320775

Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Latest version (submitted March 16, 2015) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	October 3, 2006	Outcome Measures, Conditions, Study Status, Eligibility, Study Description and Study Identification
3	○	○	July 25, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
4	○	○	January 23, 2009	Recruitment Status, Study Status, Study Design, Arms and Interventions, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
5	○	○	April 29, 2009	Study Status, Arms and Interventions, Study Description and Sponsor/Collaborators
6	○	○	January 26, 2010	Study Status
7	○	○	January 25, 2011	Study Status
8	○	○	June 8, 2011	Study Status
9	◉	◉	March 16, 2015	Sponsor/Collaborators, Study Status and References

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320775

Submitted Date: March 16, 2015 (v9)

Study Identification

Unique Protocol ID: VGFT-OD-0502

Brief Title: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: March 2015

Overall Status:	Completed
Study Start:	June 2005
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	March 16, 2015
Last Update Posted:	March 18, 2015 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	The purpose of this trial is to assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This study consists of three parts, Part A, Part B and Part C. Part A is a dose escalation. Part B was terminated early. The (one) subject who received Macugen is not discussed in this website. Part C had

subjects receive one of two doses of VEGF Trap (0.15 mg or 4.0 mg).

This is the first study in which human subjects received intravitreal injections of VEGF Trap in a study eye.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1
Interventional Study Model:	Parallel Assignment
Number of Arms:	3
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	51 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Experimental: Part A Part A: An open label study in which six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. The total volume of each injection will be 100 µL. Enrollment in new dose levels will not begin until all patients in the preceding dose level have completed Visit 5 (Day 15).	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part B Part B: A controlled, prospective, randomized, double-masked study in which up to 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive a single ITV injection of2.0 mg/eye VEGF Trap (or the MTD if reached prior to 2.0 mg) followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Enrollment into Part B will begin 2 weeks after the last subject to receive the 2.0 mg/eye dose in Part A has been observed for 15 days and it has been determined that the safety profile of VEGF Trap at this dose level is adequate to support expansion of dosing at this dose level. The dose of pegaptanib sodium will be 0.3 mg, according to the package insert.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Arms	Assigned Interventions
Active Comparator: Part C Part C: A controlled, prospective, randomized, double-masked study in which approximately 30 subjects meeting eligibility criteria will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. Initiation of Part C is contingent upon the 4.0 mg dose being adequately tolerated in Part A.	Drug: VEGF Trap Part A: Six successive cohorts of 3-6 patients each with neovascular AMD will receive a single intravitreal (ITV) injection of 0.05, 0.15, 0.5, 1.0, 2.0, or 4.0 mg of VEGF Trap into the study eye. Part B: Up to 30 subjects will be randomly assigned in a 1:1 ratio to receive a single of 2.0 mg/eye VEGF Trap followed by 1 sham injection six weeks later, or an initial dose of 0.3 mg pegaptanib sodium into the study eye, followed by a second dose six weeks later. Part C: Approximately 30 subjects will be randomly assigned in a 1:1 ratio to receive up to two ITV injections of either 0.15 or 4.0 mg/eye VEGF Trap. After completion of Visit 8 (Day 57), patients from all parts of the study, may be eligible to continue in Open-label Extension and will receive 4.0 mg of VEGF Trap. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, bioeffect
   From baseline to Day 43

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on excess central retinal/lesion thickness
   From baseline to Day 43
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity
   From baseline to Day 43
4. Extent of CNV leakage

From baseline to Day 43

5. Anti-VEGF Trap antibodies in the systemic circulation
   From baseline to Day 43
6. Plasma levels of VEGF Trap
   From baseliene to Day 43

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal/lesion thickness ≥ 250µm as measured by optical coherence tomography (OCT).
- ETDRS best-corrected visual acuity of:
  - 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography.

Exclusion Criteria:

- Prior treatment with VEGF Trap, bevacizumab or ranibizumab.
- Any investigational agent within 12 weeks of Visit 2 (Day 1).
- Presence of other causes of CNV.
- Active ocular infection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Retina Centers, PC
Tuscon, Arizona, United States, 85704

United States, California

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28120

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

IPDSharing

Plan to Share IPD:

References

Citations: **[Study Results]** Nguyen QD, Campochiaro PA, Shah SM, Browning DJ, Hudson HL, Sonkin PL, Hariprasad SM, Kaiser PK, Slakter J, Haller JA, Do DV, Mieler W, Chu K, Ingerman A, Vitti R, Berliner AJ, Cedarbaum J; Clear-It 1 Investigators. Evaluation of very high- and very low-dose intravitreal aflibercept in patients with neovascular age-related macular degeneration. J Ocul Pharmacol Ther. 2012 Dec;28(6):581-8. doi: 10.1089/jop.2011.0261. Epub 2012 Jul 9. PubMed 22775078

[Study Results] Do DV, Schmidt-Erfurth U, Gonzalez VH, Gordon CM, Tolentino M, Berliner AJ, Vitti R, Rückert R, Sandbrink R, Stein D, Yang K, Beckmann K, Heier JS. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. 2011 Sep;118(9):1819-26. doi: 10.1016/j.ophtha.2011.02.018. Epub 2011 May 5. PubMed 21546089

Links: URL: http://www.ncbi.nlm.nih.gov/pubmed/22775078
Description: Related Info

URL: http://www.ncbi.nlm.nih.gov/pubmed/21546089
Description: Related Info

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	◉	◉	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: December 1, 2011 (v9)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	December 2011
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	July 2007 [Actual]
Study Completion:	June 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Certification/Extension First Submitted:	November 30, 2010
Certification/Extension First Submitted that Met QC Criteria:	November 30, 2010
Certification/Extension First Posted:	December 2, 2010 [Estimate]
Last Update Submitted that Met QC Criteria:	December 1, 2011
Last Update Posted:	December 8, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD. The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.
Detailed Description:	This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period. After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	1
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized

Enrollment: 159 [Actual]

Arms and Interventions

Arms	Assigned Interventions
1 This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Beginning with Week 16, all patients will be evaluated every 4 weeks for continued dosing for up to one year. The fellow eye may also be eligible for treatment with VEGF Trap beginning at this	Drug: VEGF Trap Subjects in Group A will receive 2 ITV injections of 0.5 mg VEGF Trap at 12-week intervals; Group B subjects will receive 4 ITV injections of 0.5 mg VEGF Trap at 4-week intervals; Group C subjects will receive 2 injections of 2.0 mg VEGF Trap at 12-week intervals; Group D subjects will receive 4 injections of 2.0 mg VEGF Trap at 4-week intervals, and Group E subjects will receive 2 injections of 4.0 mg VEGF Trap at 12-week intervals. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)
   From baseline to week 12

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life
   From baseline to week 12

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director

Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants
Phoenix, Arizona, United States, 85020

Retina Centers, PC
Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group
Beverly Hills, California, United States, 90211

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center
Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute
Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston
Boston, Massachusetts, United States, 02114

New England Retina Consultants PC

West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	◉	◉	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: April 20, 2011 (v8)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	April 2011
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	July 2007 [Actual]
Study Completion:	June 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Certification/Extension First Submitted:	November 30, 2010
Certification/Extension First Submitted that Met QC Criteria:	November 30, 2010
Certification/Extension First Posted:	December 2, 2010 [Estimate]
Last Update Submitted that Met QC Criteria:	April 20, 2011
Last Update Posted:	April 28, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary: This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	1
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized

Enrollment: 159 [Actual]

Arms and Interventions

Arms	Assigned Interventions
1 This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Beginning with Week 16, all patients will be evaluated every 4 weeks for continued dosing for up to one year. The fellow eye may also be eligible for treatment with VEGF Trap beginning at this	Drug: VEGF Trap Subjects in Group A will receive 2 ITV injections of 0.5 mg VEGF Trap at 12-week intervals; Group B subjects will receive 4 ITV injections of 0.5 mg VEGF Trap at 4-week intervals; Group C subjects will receive 2 injections of 2.0 mg VEGF Trap at 12-week intervals; Group D subjects will receive 4 injections of 2.0 mg VEGF Trap at 4-week intervals, and Group E subjects will receive 2 injections of 4.0 mg VEGF Trap at 12-week intervals. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)
   From baseline to week 12

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life
   From baseline to week 12

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director

Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants
Phoenix, Arizona, United States, 85020

Retina Centers, PC
Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group
Beverly Hills, California, United States, 90211

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center
Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute
Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston
Boston, Massachusetts, United States, 02114

New England Retina Consultants PC

West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	◉	◉	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: November 30, 2010 (v7)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	November 2010
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Certification/Extension First Submitted:	November 30, 2010
Certification/Extension First Submitted that Met QC Criteria:	November 30, 2010
Certification/Extension First Posted:	December 2, 2010 [Estimate]
Last Update Submitted that Met QC Criteria:	November 30, 2010
Last Update Posted:	December 2, 2010 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary: This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	1
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized

Enrollment: 159 [Actual]

Arms and Interventions

Arms	Assigned Interventions
1 This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Beginning with Week 16, all patients will be evaluated every 4 weeks for continued dosing for up to one year. The fellow eye may also be eligible for treatment with VEGF Trap beginning at this	Drug: VEGF Trap Subjects in Group A will receive 2 ITV injections of 0.5 mg VEGF Trap at 12-week intervals; Group B subjects will receive 4 ITV injections of 0.5 mg VEGF Trap at 4-week intervals; Group C subjects will receive 2 injections of 2.0 mg VEGF Trap at 12-week intervals; Group D subjects will receive 4 injections of 2.0 mg VEGF Trap at 4-week intervals, and Group E subjects will receive 2 injections of 4.0 mg VEGF Trap at 12-week intervals. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)
   From baseline to week 12

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life
   From baseline to week 12

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director

Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants
Phoenix, Arizona, United States, 85020

Retina Centers, PC
Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group
Beverly Hills, California, United States, 90211

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center
Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute
Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston
Boston, Massachusetts, United States, 02114

New England Retina Consultants PC

West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:	
Links:	
Available IPD/Information:	

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	◉	◉	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: April 28, 2009 (v6)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	April 2009
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	April 28, 2009
Last Update Posted:	April 29, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms: 1

Masking: Triple (Participant, Care Provider, Investigator)

Allocation: Randomized

Enrollment: 159 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
1 This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Beginning with Week 16, all patients will be evaluated every 4 weeks for continued dosing for up to one year. The fellow eye may also be eligible for treatment with VEGF Trap beginning at this	Drug: VEGF Trap Subjects in Group A will receive 2 ITV injections of 0.5 mg VEGF Trap at 12-week intervals; Group B subjects will receive 4 ITV injections of 0.5 mg VEGF Trap at 4-week intervals; Group C subjects will receive 2 injections of 2.0 mg VEGF Trap at 12-week intervals; Group D subjects will receive 4 injections of 2.0 mg VEGF Trap at 4-week intervals, and Group E subjects will receive 2 injections of 4.0 mg VEGF Trap at 12-week intervals. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)
   From baseline to week 12

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life
   From baseline to week 12

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants

Phoenix, Arizona, United States, 85020

Retina Centers, PC
Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group
Beverly Hills, California, United States, 90211

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center
Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute
Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston
Boston, Massachusetts, United States, 02114

New England Retina Consultants PC
West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	◉	◉	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: January 23, 2009 (v5)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF-Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	January 2009
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 23, 2009
Last Update Posted:	January 27, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms: 1

Masking: Triple (Participant, Care Provider, Investigator)

Allocation: Randomized

Enrollment: 159 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
1 This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Beginning with Week 16, all patients will be evaluated every 4 weeks for continued dosing for up to one year. The fellow eye may also be eligible for treatment with VEGF Trap beginning at this	Drug: VEGF Trap Subjects in Group A will receive 2 ITV injections of 0.5 mg VEGF Trap at 12-week intervals; Group B subjects will receive 4 ITV injections of 0.5 mg VEGF Trap at 4-week intervals; Group C subjects will receive 2 injections of 2.0 mg VEGF Trap at 12-week intervals; Group D subjects will receive 4 injections of 2.0 mg VEGF Trap at 4-week intervals, and Group E subjects will receive 2 injections of 4.0 mg VEGF Trap at 12-week intervals. Other Names: • Aflibercept

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)
   From baseline to week 12

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life
   From baseline to week 12

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants

Phoenix, Arizona, United States, 85020

Retina Centers, PC

Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group

Beverly Hills, California, United States, 90211

Loma Linda University Health Care

Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center

Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago

Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute

Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine

Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston

Boston, Massachusetts, United States, 02114

New England Retina Consultants PC

West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification
4	◉	◉	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: July 24, 2007 (v4)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)

Official Title:	A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	July 2007
Overall Status:	Active, not recruiting
Study Start:	April 2006
Primary Completion:	
Study Completion:	
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	July 24, 2007
Last Update Posted:	July 26, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary: This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms:

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 150

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).

- Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
- Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
- Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).

- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director

Locations: **United States, Arizona**

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Irvine, California, United States, 92697

Loma Linda, California, United States, 92354

Menlo Park, California, United States, 94025

Palm Springs, California, United States, 92262

United States, Florida

Ft. Myers, Florida, United States, 33912

Lakeland, Florida, United States, 33805

Oakland Park, Florida, United States, 33334

Orlando, Florida, United States, 32803

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Chicago, Illinois, United States, 60637

Glenview, Illinois, United States, 60025

United States, Indiana

Indianapolis, Indiana, United States, 46280

United States, Maryland

Baltimore, Maryland, United States, 21204

Baltimore, Maryland, United States, 21287

United States, Massachusetts

Boston, Massachusetts, United States, 02114

Peabody, Massachusetts, United States

West Springfield, Massachusetts, United States, 10189

United States, Michigan

Ann Arbor, Michigan, United States, 48105

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Great Neck, New York, United States, 11021

New York, New York, United States, 10032

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, Pennsylvania

Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Houston, Texas, United States, 77030

San Antonio, Texas, United States, 78240

United States, Wisconsin

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
3	◉	◉	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: October 3, 2006 (v3)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)

Official Title:	A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	August 2006
Overall Status:	Recruiting
Study Start:	April 2006
Primary Completion:	
Study Completion:	
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	October 3, 2006
Last Update Posted:	October 4, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary: This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (ITV) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions: Macular Degeneration

Keywords: Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms:

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 150

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (optical coherence tomography [OCT], fluorescein angiography, visual acuity)

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).

- Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
- Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
- Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).

- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Central Contact: Regeneron
Email: VEGF.Trap@regeneron.com

Locations: **United States, Arizona**

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]
Tucson, Arizona, United States, 85704

United States, California

[Recruiting]
Beverly Hills, California, United States, 90211

[Not yet recruiting]
Irvine, California, United States, 92697

[Not yet recruiting]
Loma Linda, California, United States, 92354

[Not yet recruiting]
Menlo Park, California, United States, 94025

[Recruiting]

Palm Springs, California, United States, 92262

United States, Florida

[Recruiting]
Ft. Myers, Florida, United States, 33912

[Recruiting]
Lakeland, Florida, United States, 33805

[Recruiting]
Oakland Park, Florida, United States, 33334

[Not yet recruiting]
Orlando, Florida, United States, 32803

United States, Georgia

[Recruiting]
Augusta, Georgia, United States, 30909

United States, Illinois

[Not yet recruiting]
Chicago, Illinois, United States, 60637

[Not yet recruiting]
Glenview, Illinois, United States, 60025

United States, Indiana

[Recruiting]
Indianapolis, Indiana, United States, 46280

United States, Maryland

[Not yet recruiting]
Baltimore, Maryland, United States, 21204

[Recruiting]
Baltimore, Maryland, United States, 21287

United States, Massachusetts

[Recruiting]

Boston, Massachusetts, United States, 02114

[Recruiting]

Peabody, Massachusetts, United States

[Recruiting]

West Springfield, Massachusetts, United States, 10189

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

United States, New Jersey

[Recruiting]

Toms River, New Jersey, United States, 08755

United States, New York

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Recruiting]

New York, New York, United States, 10032

United States, North Carolina

[Recruiting]

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

[Not yet recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Recruiting]

Portland, Oregon, United States, 97210

United States, Pennsylvania

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Houston, Texas, United States, 77030

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Wisconsin

[Not yet recruiting]

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320788

Safety and Efficacy of Repeated Intravitreal Administration of VEGF Trap in Patients With Wet AMD

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	◉	◉	August 1, 2006	Contacts/Locations and Study Status
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification

Version	A	B	Submitted Date	Changes
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	○	○	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: August 1, 2006 (v2)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of VEGF Trap in Patients With Wet AMD

Official Title: A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification:	August 2006
Overall Status:	Recruiting
Study Start:	April 2006
Primary Completion:	
Study Completion:	
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	August 1, 2006
Last Update Posted:	August 3, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	The effect of intravitreally administered VEGF Trap in patients with wet AMD.

To assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of ITV injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions: Neovascular Age-Related Macular Degeneration

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms:

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 150

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety, biological effect (OCT, fluorescein angiography, visual acuity)

Secondary Outcome Measures:

2. Pharmacokinetics, immunogenicity, quality of life

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by OCT.
- ETDRS best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - PDT within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxta-scleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.

- Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Central Contact: Regeneron
Email: VEGF.Trap@regeneron.com

Locations: **United States, Arizona**

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]
Tuscon, Arizona, United States, 85704

United States, California

[Recruiting]
Beverly Hills, California, United States, 90211

[Not yet recruiting]
Irvine, California, United States, 92697

[Not yet recruiting]
Loma Linda, California, United States, 92354

[Not yet recruiting]
Menlo Park, California, United States, 94025

[Recruiting]
Palm Springs, California, United States, 92262

United States, Florida

[Recruiting]
Ft. Myers, Florida, United States, 33912

[Recruiting]

Lakeland, Florida, United States, 33805

[Recruiting]

Oakland Park, Florida, United States, 33334

[Not yet recruiting]

Orlando, Florida, United States, 32803

United States, Georgia

[Recruiting]

Augusta, Georgia, United States, 30909

United States, Illinois

[Not yet recruiting]

Chicago, Illinois, United States, 60637

[Not yet recruiting]

Glenview, Illinois, United States, 60025

United States, Indiana

[Recruiting]

Indianopolis, Indiana, United States, 46280

United States, Maryland

[Not yet recruiting]

Baltimore, Maryland, United States, 21204

[Recruiting]

Baltimore, Maryland, United States, 21287

United States, Massachusetts

[Recruiting]

Boston, Massachusetts, United States, 02114

[Recruiting]

Peabody, Massachusetts, United States

[Recruiting]

West Springfield, Massachusetts, United States, 10189

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

United States, New Jersey

[Recruiting]

Toms River, New Jersey, United States, 08755

United States, New York

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Recruiting]

New York, New York, United States, 10032

United States, North Carolina

[Recruiting]

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

[Not yet recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Recruiting]

Portland, Oregon, United States, 97210

United States, Pennsylvania

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Houston, Texas, United States, 77030

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Wisconsin

[Not yet recruiting]

Madison, Wisconsin, United States, 53705

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted January 27, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	August 1, 2006	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
3	○	○	October 3, 2006	Conditions, Study Description, Contacts/Locations, Eligibility, Outcome Measures, Study Status and Study Identification
4	○	○	July 24, 2007	Recruitment Status, Study Status and Contacts/Locations
5	○	○	January 23, 2009	Recruitment Status, Study Status, Arms and Interventions, Study Design, Contacts/Locations, Outcome Measures, Oversight, Sponsor/Collaborators and Study Identification
6	○	○	April 28, 2009	Study Status
7	○	○	November 30, 2010	Study Status
8	○	○	April 20, 2011	Study Status
9	○	○	December 1, 2011	Sponsor/Collaborators, Study Status
10	◉	◉	January 27, 2012	Arms and Interventions, Study Status, Outcome Measures, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, References, Contacts/Locations, Eligibility, Study Description and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320788

Submitted Date: January 27, 2012 (v10)

Study Identification

Unique Protocol ID: VGFT-OD-0508

Brief Title: Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)

Official Title:	A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	January 2012
Overall Status:	Completed
Study Start:	April 2006
Primary Completion:	June 2008 [Actual]
Study Completion:	August 2008 [Actual]
First Submitted:	April 28, 2006
First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Results First Submitted:	December 16, 2011
Results First Submitted that Met QC Criteria:	January 27, 2012
Results First Posted:	March 1, 2012 [Estimate]
Certification/Extension First Submitted:	November 30, 2010
Certification/Extension First Submitted that Met QC Criteria:	November 30, 2010
Certification/Extension First Posted:	December 2, 2010 [Estimate]
Last Update Submitted that	January 27, 2012

Met QC Criteria:	
Last Update Posted:	March 1, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary: This study examines the effect of intravitreally administered VEGF Trap in patients with wet AMD.

The purpose of this trial is to assess the ocular and systemic safety and tolerability of repeated intravitreal doses of VEGF Trap in patients with subfoveal choroidal neovascularization (CNV) due to AMD.

Detailed Description: This is a double masked, prospective, randomized study in which five groups of approximately 30 patients meeting the eligibility criteria will be randomly assigned in a balanced ratio to receive a series of intravitreal (IVT) injections of VEGF Trap into the study eye at 4- or 12 -week intervals over a 12-week period.

After Week 12, patients will be evaluated every 4 weeks. Patients will remain on study or may be eligible to enter a long-term extension study, in which they will continue to receive VEGF Trap.

Conditions

Conditions:	Macular Degeneration
Keywords:	Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	5
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized
Enrollment:	159 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: aflibercept injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received 0.5 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 4 week intervals through Week 12 Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q12	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received 0.5 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12. Other Names: • VEGF Trap-Eye • BAY86-5321

Arms	Assigned Interventions
Experimental: aflibercept injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received 2.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 4 week intervals through Week 12 Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q12	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received 2.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection (VEGF Trap-Eye, BAY86-5321) 4.0mg q12	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received 4.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12. Other Names: • VEGF Trap-Eye • BAY86-5321

Outcome Measures

[See Results Section]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Subfoveal CNV secondary to AMD.
- Central retinal (including lesion) thickness ≥ 300 µm as measured by Optical Coherence Tomography (OCT).
- Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity of 73 letters to 34 letters.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Day 1.
- Aphakia.
- Significant subfoveal atrophy or scarring.
- Prior treatment with the following in the study eye:
  - Subfoveal thermal laser therapy.
  - Submacular surgery or other surgical intervention for the treatment of AMD.
  - Extrafoveal laser coagulation treatment within 12 weeks prior to Day 1.
  - Photodynamic therapy (PDT) within 12 weeks prior to Visit 2 (Day 1).
  - Pegaptanib sodium (Macugen) within 8 weeks of Visit 2 (Day 1).
  - Juxtascleral steroids or anecortave acetate within 24 weeks (6 months) prior to Visit 2 (Day 1).
  - Intravitreal administration of triamcinolone acetonide or other steroids within 24 weeks prior to Visit 2 (Day 1), unless no visible residue of drug substance can be seen in the vitreous cavity using indirect ophthalmoscopy.
  - Prior systemic or intravitreal treatment with VEGF Trap, ranibizumab (Lucentis) or bevacizumab (Avastin).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase II study.

Contacts/Locations

Study Officials: Clinical Trial Management
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Associated Retina Consultants
Phoenix, Arizona, United States, 85020

Retina Centers, PC
Tucson, Arizona, United States, 85704

United States, California

Retina Vitreous Associates Medical Group
Beverly Hills, California, United States, 90211

Loma Linda University Health Care
Loma Linda, California, United States, 92354

United States, Georgia

Southeast Retina Center
Augusta, Georgia, United States, 30909

United States, Illinois

University of Chicago
Chicago, Illinois, United States, 60637

United States, Indiana

Midwest Eye Institute
Indianapolis, Indiana, United States, 46280

United States, Maryland

Johns Hopkins Hospital School of Medicine
Baltimore, Maryland, United States, 21287

United States, Massachusetts

Ophthalmic Consultants of Boston
Boston, Massachusetts, United States, 02114

New England Retina Consultants PC
West Springfield, Massachusetts, United States, 10189

United States, North Carolina

Charlotte Eye, Ear, Nose & Throat Asssociates
Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Dean A. McGee Eye Institute
Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Retina Northwest PC
Portland, Oregon, United States, 97210

United States, Pennsylvania

Retina Diagnostic and Treatment Assoc., LLC
Philadelphia, Pennsylvania, United States, 19107

United States, South Dakota

Black Hills Regional Eye Institute
Rapid City, South Dakota, United States, 57701

United States, Tennessee

Retina-Vitreous Associates, P.C.
Nashville, Tennessee, United States, 37203

United States, Texas

Vitreoretinal Consultants Scurlock Tower Texas Medical Center
Houston, Texas, United States, 77030

Medical Center Ophthamology
San Antonio, Texas, United States, 78240

IPDSharing

Plan to Share IPD:

References

Citations:

Links: URL: http://www.ncbi.nlm.nih.gov/pubmed/21640257
Description: Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration.

URL: http://www.ncbi.nlm.nih.gov/pubmed/21640258
Description: 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.

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	The study was conducted at 29 study sites in the United States. Recruitment period: May 2006 to April 2007.
Pre-assignment Details	A total of 301 participants were screened; 159 participants were randomized; 157 participants were included in both the Safety Analysis Set (SAF) and the Full Analysis Set (FAS) as all received study treatment, had baseline assessments and at least 1 post-baseline assessment.

Reporting Groups

	Description
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q4	Participants received 0.5 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 4 week intervals through Week 12.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q12	Participants received 0.5 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12.

Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q4	Participants received 2.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 4 week intervals through Week 12.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q12	Participants received 2.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 4.0mg q12	Participants received 4.0 mg of aflibercept injection (VEGF Trap-Eye, BAY86-5321) at 12 week intervals through Week 12.

Overall Study

	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q4	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg q12	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q4	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg q12	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 4.0mg q12
Started	32	32	32	32 [1]	31
Participants Received Treatment (SAF)	32	32	31 [2]	31 [2]	31
Completed	26	26	29	27	26
Not Completed	6	6	3	5	5
Adverse Event	0	0	0	1	0
Death	0	0	1	0	1
Lost to Follow-up	0	2	1	0	0
Decision by the Sponsor	1	1	0	0	1
Other	1	2	1	1	1
Physician Decision	1	1	0	0	0
Protocol Violation	0	0	0	0	1
Withdrawal by Subject	3	0	0	3	1

[1] Participants Randomized

[2] One participant in this group did not receive treatment and was not included in the SAF and FAS

Baseline Characteristics

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.

Baseline Measures

		Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants		32	32	31	31	31	157
Age Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
		79.6 (0 to 0)	78.5 (0 to 0)	74.9 (0 to 0)	79.6 (0 to 0)	78.3 (0 to 0)	78.2 (0 to 0)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
	Female	17 53.12% (0 to 0)	25 78.12% (0 to 0)	20 64.52% (0 to 0)	16 51.61% (0 to 0)	20 64.52% (0 to 0)	98 62.42%
	Male	15 46.88% (0 to 0)	7 21.88% (0 to 0)	11 35.48% (0 to 0)	15 48.39% (0 to 0)	11 35.48% (0 to 0)	59 37.58%

		Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
	Hispanic or Latino	0 0% (0 to 0)	1 3.12% (0 to 0)	2 6.45% (0 to 0)	1 3.23% (0 to 0)	0 0% (0 to 0)	4 2.55%
	Not Hispanic or Latino	32 100% (0 to 0)	31 96.88% (0 to 0)	29 93.55% (0 to 0)	30 96.77% (0 to 0)	31 100% (0 to 0)	153 97.45%
	Unknown or Not Reported	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
Race (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
	American Indian or Alaska Native	0 0% (0 to 0)	0 0% (0 to 0)	1 3.23% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.64%
	Asian	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
	Native Hawaiian or Other Pacific Islander	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
	Black or African American	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
	White	32 100% (0 to 0)	32 100% (0 to 0)	30 96.77% (0 to 0)	31 100% (0 to 0)	31 100% (0 to 0)	156 99.36%

		Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
	More than one race	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
	Unknown or Not Reported	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
Central Retinal/Lesion Thickness (CR/LT) Mean (Standard Deviation) Unit of measure: µm	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
		442.2 (0 to 0)	442.6 (0 to 0)	453.3 (0 to 0)	447.0 (0 to 0)	497.5 (0 to 0)	456.4 (0 to 0)
Best Corrected Visual Acuity (BCVA) [1] Mean (Standard Deviation) Unit of measure: letters read	Number Analyzed	32 Participants	32 Participants	31 Participants	31 Participants	31 Participants	157 Participants
		54.1 (0 to 0)	55.6 (0 to 0)	57.9 (0 to 0)	57.2 (0 to 0)	53.0 (0 to 0)	55.5 (0 to 0)
		[1] Measure Description: BCVA as Measured by 4 Meter Early Treatment Diabetic Retinopathy Study (ETDRS)eye charts/measures					

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Mean Change of CR/LT From Baseline at Week 12
Measure Description	CR/LT measured in micrometers (µm); lower individual values represent better outcomes.
Time Frame	Baseline and at Week 12

Analysis Population Description

Full Analysis Set (FAS) used for analysis, Last Observation Carried Forward (LOCF)

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Mean Change of CR/LT From Baseline at Week 12 Measure Type: Mean (Standard Deviation) Unit of Measure: µm	-153.5 (0 to 0)	-75.6 (0 to 0)	-169.2 (0 to 0)	-56.3 (0 to 0)	-139.8 (0 to 0)	-118.8 (0 to 0)

2. Secondary Outcome Measure:

Measure Title	Mean Percent Change of CR/LT From Baseline at Week 12
Measure Description	CR/LT measured in micrometers (µm); a more negative percentage represents a better outcome
Time Frame	Baseline and at Week 12

Analysis Population Description

FAS used for analysis, LOCF

Reporting Groups

	Description

Aflibercept Injection 0.5mg q4	Participants received 0.5mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Mean Percent Change of CR/LT From Baseline at Week 12 Measure Type: Mean (Standard Deviation) Unit of Measure: percent change	-32.4 (0 to 0)	-15.2 (0 to 0)	-33.2 (0 to 0)	-10.3 (0 to 0)	-21.1 (0 to 0)	-22.5 (0 to 0)

3. Secondary Outcome Measure:

Measure Title	Mean Change in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) From Baseline at Week 12
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning
Time Frame	Baseline and at week 12

Analysis Population Description

FAS used for analysis, LOCF

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Mean Change in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) From Baseline at Week 12 Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	8.8 (0 to 0)	3.8 (0 to 0)	8.3 (0 to 0)	5.2 (0 to 0)	2.6 (0 to 0)	5.7 (0 to 0)

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score From Baseline at Week 12
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning
Time Frame	At Week 12

Analysis Population Description

FAS used for analysis, LOCF

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score From Baseline at Week 12 Measure Type: Number Unit of Measure: percentage of participants	18.8 (0 to 0)	21.9 (0 to 0)	25.8 (0 to 0)	16.1 (0 to 0)	9.7 (0 to 0)	18.5 (0 to 0)

5. Post-Hoc Outcome Measure:

Measure Title	Mean Change of CR/LT From Baseline at Week 16
Measure Description	CR/LT measured in micrometers (µm); lower individual values represent better outcomes
Time Frame	Baseline and at Week 16

Analysis Population Description

FAS used for analysis, LOCF

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Mean Change of CR/LT From Baseline at Week 16 Measure Type: Mean (Standard Deviation) Unit of Measure: µm	-163.3 (0 to 0)	-139.6 (0 to 0)	-182.7 (0 to 0)	-107.4 (0 to 0)	-208.6 (0 to 0)	-160.2 (0 to 0)

6. Post-Hoc Outcome Measure:

Measure Title	Mean Change in BCVA as Measured by ETDRS From Baseline at Week 16
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning
Time Frame	Baseline and at Week 16

Analysis Population Description

FAS used for analysis, LOCF

Reporting Groups

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.
Total	

Measured Values

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12	Total
Overall Number of Participants Analyzed	32	32	31	31	31	157
Mean Change in BCVA as Measured by ETDRS From Baseline at Week 16 Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	9.3 (0 to 0)	5.6 (0 to 0)	10.0 (0 to 0)	4.3 (0 to 0)	3.9 (0 to 0)	6.6 (0 to 0)

Reported Adverse Events

Time Frame	Adverse events (AEs) considered related to study treatment were followed until resolution or until the event was considered chronic or stable.
Adverse Event Reporting Description	Safety was assessed through reported AEs, clinical laboratory test results, vital signs, and ophthalmic examinations

Reporting Groups

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1318 of 2000

	Description
Aflibercept Injection 0.5mg q4	Participants received 0.5 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 0.5mg q12	Participants received 0.5 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 2.0mg q4	Participants received 2.0 mg of aflibercept injection at 4 week intervals through Week 12.
Aflibercept Injection 2.0mg q12	Participants received 2.0 mg of aflibercept injection at 12 week intervals through Week 12.
Aflibercept Injection 4.0mg q12	Participants received 4.0 mg of aflibercept injection at 12 week intervals through Week 12.

All-Cause Mortality

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/	/

Serious Adverse Events

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	11/	5/	10/	7/	2/
Cardiac disorders					
ANGINA PECTORIS [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
ATRIAL FIBRILLATION [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
ATRIOVENTRICULAR BLOCK COMPLETE [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
BRADYCARDIA [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
CARDIAC FAILURE CONGESTIVE [A†]	1/32 (3.12%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
CORONARY ARTERY DISEASE [A†]	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
Eye disorders					
RETINAL DETACHMENT [A [1]†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
UVEITIS [A [2]†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
VISUAL ACUITY REDUCED [A [1]†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Gastrointestinal disorders					
DYSKINESIA OESOPHAGEAL [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
INTESTINAL OBSTRUCTION [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
SMALL INTESTINAL OBSTRUCTION [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
VOLVULUS [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
General disorders					
ASTHENIA [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
NON-CARDIAC CHEST PAIN [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Infections and infestations					
BRONCHITIS [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	1/31 (3.23%)	0/31 (0%)
CELLULITIS [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
GASTROENTERITIS [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
PNEUMONIA [A†]	2/32 (6.25%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
URINARY TRACT INFECTION [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	1/31 (3.23%)	0/31 (0%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
Injury, poisoning and procedural complications					
FALL [A†]	1/32 (3.12%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
HIP FRACTURE [A†]	0/32 (0%)	1/32 (3.12%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
SKIN LACERATION [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)
SYNOVIAL RUPTURE [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Investigations					
INTRAOCULAR PRESSURE INCREASED [A [1]†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
Musculoskeletal and connective tissue disorders					
BACK PAIN [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
OSTEOARTHRITIS [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
SPINAL OSTEOARTHRITIS [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
BRAIN NEOPLASM MALIGNANT [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
COLON CANCER [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
METASTASES TO LUNG [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)
NON-HODGKIN'S LYMPHOMA [A†]	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
PANCREATIC CARCINOMA [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
SQUAMOUS CELL CARCINOMA [A†]	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
THYROID NEOPLASM [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
TRANSITIONAL CELL CARCINOMA A†	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)
Nervous system disorders					
CAROTID ARTERY OCCLUSION A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
CEREBROVASCULAR ACCIDENT A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
COORDINATION ABNORMAL A†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
DYSARTHRIA A†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
SPINAL CORD DISORDER A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
TRANSIENT ISCHAEMIC ATTACK A†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
Renal and urinary disorders					
RENAL FAILURE A†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
STRESS INCONTINENCE A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
URINARY RETENTION A†	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders					
CHRONIC OBSTRUCTIVE PULMONARY DISEASE A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
PNEUMONIA ASPIRATION A†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
PULMONARY EMBOLISM A†	0/32 (0%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	0/31 (0%)
PULMONARY HYPERTENSION A†	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
Surgical and medical procedures					
PILONIDAL SINUS REPAIR A†	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Vascular disorders					
DEEP VEIN THROMBOSIS A†	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	0/31 (0%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA 10.0

[1] Fellow Eye

[2] Study Eye

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	26/	25/	27/	22/	22/
Blood and lymphatic system disorders					
ANAEMIA A†	0/32 (0%)	1/32 (3.12%)	3/31 (9.68%)	0/31 (0%)	0/31 (0%)
Cardiac disorders					
ANGINA PECTORIS A†	2/32 (6.25%)	0/32 (0%)	1/31 (3.23%)	1/31 (3.23%)	0/31 (0%)
BRADYCARDIA A†	1/32 (3.12%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
Eye disorders					
BLEPHARITIS A [1]†	2/32 (6.25%)	0/32 (0%)	2/31 (6.45%)	3/31 (9.68%)	1/31 (3.23%)
CATARACT A [1]†	0/32 (0%)	1/32 (3.12%)	1/31 (3.23%)	1/31 (3.23%)	2/31 (6.45%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
CATARACT NUCLEAR [A] [1]†	3/32 (9.38%)	0/32 (0%)	2/31 (6.45%)	1/31 (3.23%)	0/31 (0%)
CATARACT SUBCAPSULAR [A] [1]†	0/32 (0%)	2/32 (6.25%)	0/31 (0%)	1/31 (3.23%)	2/31 (6.45%)
CHOROIDAL NEOVASCULARISATION [A] [1]†	0/32 (0%)	1/32 (3.12%)	2/31 (6.45%)	1/31 (3.23%)	0/31 (0%)
CONJUNCTIVAL HAEMORRHAGE [A] [1]†	2/32 (6.25%)	0/32 (0%)	2/31 (6.45%)	2/31 (6.45%)	1/31 (3.23%)
DETACHMENT OF RETINAL PIGMENT EPITHELIUM [A] [1]†	2/32 (6.25%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
DRY EYE [A] [1]†	1/32 (3.12%)	0/32 (0%)	1/31 (3.23%)	2/31 (6.45%)	0/31 (0%)
EYE INFLAMMATION [A] [2]†	2/32 (6.25%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	1/31 (3.23%)
EYE IRRITATION [A] [2]†	5/32 (15.62%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	1/31 (3.23%)
EYE PAIN [A] [2]†	5/32 (15.62%)	2/32 (6.25%)	4/31 (12.9%)	1/31 (3.23%)	3/31 (9.68%)
FOREIGN BODY SENSATION IN EYES [A] [2]†	3/32 (9.38%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
LACRIMATION DECREASED [A] [2]†	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	2/31 (6.45%)
LACRIMATION INCREASED [A] [1]†	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	2/31 (6.45%)
MACULAR DEGENERATION [A] [2]†	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	2/31 (6.45%)
MACULOPATHY [A] [2]†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	2/31 (6.45%)	1/31 (3.23%)
PHOTOPSIA [A] [2]†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	2/31 (6.45%)	3/31 (9.68%)
PUNCTATE KERATITIS [A] [2]†	0/32 (0%)	0/32 (0%)	1/31 (3.23%)	2/31 (6.45%)	2/31 (6.45%)
REFRACTION DISORDER [A] [1]†	1/32 (3.12%)	4/32 (12.5%)	1/31 (3.23%)	1/31 (3.23%)	3/31 (9.68%)
RETINAL DEPIGMENTATION [A] [2]†	2/32 (6.25%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
RETINAL HAEMORRHAGE [A] [1]†	0/32 (0%)	2/32 (6.25%)	1/31 (3.23%)	3/31 (9.68%)	0/31 (0%)
RETINAL OEDEMA [A] [1]†	1/32 (3.12%)	2/32 (6.25%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
RETINAL PIGMENT EPITHELIOPATHY [A] [1]†	2/32 (6.25%)	3/32 (9.38%)	0/31 (0%)	1/31 (3.23%)	1/31 (3.23%)
SUBRETINAL FIBROSIS [A] [2]†	2/32 (6.25%)	1/32 (3.12%)	1/31 (3.23%)	2/31 (6.45%)	2/31 (6.45%)
VISION BLURRED [A] [2]†	2/32 (6.25%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
VISUAL ACUITY REDUCED [A] [1]†	1/32 (3.12%)	1/32 (3.12%)	4/31 (12.9%)	1/31 (3.23%)	1/31 (3.23%)
VISUAL DISTURBANCE [A] [2]†	2/32 (6.25%)	1/32 (3.12%)	0/31 (0%)	2/31 (6.45%)	3/31 (9.68%)
VITREOUS DETACHMENT [A] [1]†	4/32 (12.5%)	1/32 (3.12%)	2/31 (6.45%)	3/31 (9.68%)	4/31 (12.9%)
VITREOUS FLOATERS [A] [1]†	2/32 (6.25%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	1/31 (3.23%)
Gastrointestinal disorders					
CONSTIPATION [A]†	5/32 (15.62%)	1/32 (3.12%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
DIARRHOEA [A]†	1/32 (3.12%)	1/32 (3.12%)	0/31 (0%)	1/31 (3.23%)	2/31 (6.45%)
FLATULENCE [A]†	0/32 (0%)	2/32 (6.25%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
NAUSEA [A]†	3/32 (9.38%)	0/32 (0%)	0/31 (0%)	1/31 (3.23%)	1/31 (3.23%)
General disorders					
CHEST PAIN [A]†	2/32 (6.25%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Immune system disorders					
SEASONAL ALLERGY [A]†	4/32 (12.5%)	2/32 (6.25%)	0/31 (0%)	0/31 (0%)	1/31 (3.23%)
Infections and infestations					
BRONCHITIS [A]†	5/32 (15.62%)	2/32 (6.25%)	1/31 (3.23%)	1/31 (3.23%)	3/31 (9.68%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
CELLULITIS [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	2/31 (6.45%)	1/31 (3.23%)
CYSTITIS [A†]	2/32 (6.25%)	0/32 (0%)	1/31 (3.23%)	1/31 (3.23%)	0/31 (0%)
GASTROENTERITIS VIRAL [A†]	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	1/31 (3.23%)
HERPES ZOSTER [A†]	0/32 (0%)	2/32 (6.25%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
INFLUENZA [A†]	0/32 (0%)	2/32 (6.25%)	2/31 (6.45%)	0/31 (0%)	2/31 (6.45%)
NASOPHARYNGITIS [A†]	3/32 (9.38%)	1/32 (3.12%)	3/31 (9.68%)	1/31 (3.23%)	2/31 (6.45%)
PNEUMONIA [A†]	3/32 (9.38%)	0/32 (0%)	2/31 (6.45%)	1/31 (3.23%)	1/31 (3.23%)
RHINOVIRUS INFECTION [A†]	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
SINUSITIS [A†]	2/32 (6.25%)	1/32 (3.12%)	2/31 (6.45%)	1/31 (3.23%)	3/31 (9.68%)
TOOTH ABSCESS [A†]	1/32 (3.12%)	1/32 (3.12%)	1/31 (3.23%)	2/31 (6.45%)	0/31 (0%)
UPPER RESPIRATORY TRACT INFECTION [A†]	3/32 (9.38%)	1/32 (3.12%)	2/31 (6.45%)	6/31 (19.35%)	3/31 (9.68%)
URINARY TRACT INFECTION [A†]	1/32 (3.12%)	3/32 (9.38%)	6/31 (19.35%)	1/31 (3.23%)	2/31 (6.45%)
VULVOVAGINAL MYCOTIC INFECTION [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	2/31 (6.45%)	1/31 (3.23%)
Injury, poisoning and procedural complications					
FALL [A†]	2/32 (6.25%)	1/32 (3.12%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
JOINT SPRAIN [A†]	0/32 (0%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	2/31 (6.45%)
Investigations					
BLOOD CREATININE INCREASED [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	2/31 (6.45%)	1/31 (3.23%)
BLOOD GLUCOSE INCREASED [A†]	0/32 (0%)	2/32 (6.25%)	1/31 (3.23%)	1/31 (3.23%)	0/31 (0%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
BLOOD UREA INCREASED [A†]	0/32 (0%)	1/32 (3.12%)	0/31 (0%)	2/31 (6.45%)	0/31 (0%)
INTRAOCULAR PRESSURE INCREASED [A [1]†]	1/32 (3.12%)	3/32 (9.38%)	3/31 (9.68%)	2/31 (6.45%)	1/31 (3.23%)
Metabolism and nutrition disorders					
DEHYDRATION [A†]	1/32 (3.12%)	1/32 (3.12%)	2/31 (6.45%)	0/31 (0%)	1/31 (3.23%)
GOUT [A†]	1/32 (3.12%)	2/32 (6.25%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
HYPERCHOLESTEROLAEMIA [A†]	4/32 (12.5%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Musculoskeletal and connective tissue disorders					
BACK PAIN [A†]	1/32 (3.12%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
OSTEOARTHRITIS [A†]	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	1/31 (3.23%)
Nervous system disorders					
DEMENTIA ALZHEIMER'S TYPE [A†]	0/32 (0%)	2/32 (6.25%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
DIZZINESS [A†]	1/32 (3.12%)	0/32 (0%)	2/31 (6.45%)	1/31 (3.23%)	0/31 (0%)
HEADACHE [A†]	1/32 (3.12%)	3/32 (9.38%)	1/31 (3.23%)	0/31 (0%)	1/31 (3.23%)
SINUS HEADACHE [A†]	1/32 (3.12%)	2/32 (6.25%)	2/31 (6.45%)	0/31 (0%)	2/31 (6.45%)
Psychiatric disorders					
ANXIETY [A†]	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
DEPRESSION [A†]	0/32 (0%)	1/32 (3.12%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)
INSOMNIA [A†]	2/32 (6.25%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders					
COUGH [A†]	2/32 (6.25%)	1/32 (3.12%)	2/31 (6.45%)	1/31 (3.23%)	2/31 (6.45%)

	Aflibercept Injection 0.5mg q4	Aflibercept Injection 0.5mg q12	Aflibercept Injection 2.0mg q4	Aflibercept Injection 2.0mg q12	Aflibercept Injection 4.0mg q12
DYSPNOEA A†	2/32 (6.25%)	0/32 (0%)	1/31 (3.23%)	2/31 (6.45%)	0/31 (0%)
PHARYNGOLARYNGEAL PAIN A†	1/32 (3.12%)	0/32 (0%)	0/31 (0%)	0/31 (0%)	2/31 (6.45%)
Skin and subcutaneous tissue disorders					
RASH A†	2/32 (6.25%)	0/32 (0%)	1/31 (3.23%)	0/31 (0%)	1/31 (3.23%)
Vascular disorders					
HYPERTENSION A†	6/32 (18.75%)	1/32 (3.12%)	2/31 (6.45%)	0/31 (0%)	3/31 (9.68%)
HYPOTENSION A†	0/32 (0%)	0/32 (0%)	2/31 (6.45%)	0/31 (0%)	0/31 (0%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA 10.0

[1] Fellow Eye

[2] Study Eye

Limitations and Caveats

This is a phase 2 study with small numbers of patients per group limiting the conclusions that can be drawn from the resulting data.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Clinical Trials Administrator
Organization: Regeneron Pharmaceuticals, Inc.
Phone:
Email: clinicaltrials@regeneron.com

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320814

Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Latest version (submitted June 8, 2011) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	September 6, 2006	Recruitment Status, Study Status and Contacts/Locations
3	○	○	January 5, 2009	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Oversight, Contacts/Locations, Study Design and Sponsor/Collaborators

Version	A	B	Submitted Date	Changes
4	○	○	January 25, 2011	Study Status
5	◉	◉	June 8, 2011	Study Status

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320814

Submitted Date: June 8, 2011 (v5)

Study Identification

Unique Protocol ID: VGFT-OD-0512

Brief Title: Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients With Diabetic Macular Edema

Secondary IDs:

Study Status

Record Verification: June 2011

Overall Status: Completed

Study Start: April 2006

Primary Completion: August 2006 [Actual]

Study Completion: August 2007 [Actual]

First Submitted: April 28, 2006

First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	June 8, 2011
Last Update Posted:	June 10, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with diabetic macular edema.
Detailed Description:	This is an open label study. Initially, 5 patients with DME will receive an ITV injection of VEGF Trap into the study eye. Additional patients may be enrolled at the same or additional dose levels. Patients will be observed for six weeks following the injection for assessments of ocular and systemic safety.

Conditions

Conditions:	Diabetic Macular Edema
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase: Phase 1

Interventional Study Model: Single Group Assignment

Number of Arms: 1

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 5 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1	Drug: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1

Outcome Measures

Primary Outcome Measures:

1. To assess the ocular and systemic safety and tolerability of a single intravitreal (IVT) injection of VEGF Trap-Eye in patients with diabetic macular edema (DME)
   Assessments for safety and tolerablity are performed at each visit (Visit 1 - Visit 10)

Secondary Outcome Measures:

2. To obtain a preliminary assessment of the effect of a single dose of VEGF Trap-Eye on central retinal thickness (CRT) at the center point as determined by optical coherence tomography (OCT)
   Assessments for CRT are performed at each visit (Visit 1 - Visit 10) by means of OCT.
3. To obtain a preliminary assessment of the effect of a single IVT administration of VEGF Trap-Eye on visual acuity
   Assessments for visual acuity are performed at each visit (Visit 1 - Visit 10).

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosis of diabetes mellitus (type 1 or type 2).
- Best corrected E-ETDRS visual acuity score of ≥ 24 letters (i.e., 20/320 or better) and ≤ 73 letters (i.e., 20/40 or worse).
- On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.
- Retinal Thickness at the center point ≥ 250 microns.
- Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Visit 2 (Day 1).
- Macular edema due to causes other than diabetic macular edema. An eye should be considered ineligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.
- An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).
- An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase 1 study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Maryland**

Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte, North Carolina, United States, 28210

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320814

Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Latest version (submitted June 8, 2011) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	September 6, 2006	Recruitment Status, Study Status and Contacts/Locations
3	○	○	January 5, 2009	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Oversight, Contacts/Locations, Study Design and Sponsor/Collaborators

Version	A	B	Submitted Date	Changes
4	◉	◉	January 25, 2011	Study Status
5	○	○	June 8, 2011	Study Status

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320814

Submitted Date: January 25, 2011 (v4)

Study Identification

Unique Protocol ID: VGFT-OD-0512

Brief Title: Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients With Diabetic Macular Edema

Secondary IDs:

Study Status

Record Verification: January 2011

Overall Status: Completed

Study Start: April 2006

Primary Completion: August 2006 [Actual]

Study Completion: August 2007 [Actual]

First Submitted: April 28, 2006

First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 25, 2011
Last Update Posted:	January 26, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with diabetic macular edema.
Detailed Description:	This is an open label study. Initially, 5 patients with DME will receive an ITV injection of VEGF Trap into the study eye. Additional patients may be enrolled at the same or additional dose levels. Patients will be observed for six weeks following the injection for assessments of ocular and systemic safety.

Conditions

Conditions:	Diabetic Macular Edema
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase: Phase 1

Interventional Study Model: Single Group Assignment

Number of Arms: 1

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 5 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1	Drug: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1

Outcome Measures

Primary Outcome Measures:

1. To assess the ocular and systemic safety and tolerability of a single intravitreal (IVT) injection of VEGF Trap-Eye in patients with diabetic macular edema (DME)
   Assessments for safety and tolerablity are performed at each visit (Visit 1 - Visit 10)

Secondary Outcome Measures:

2. To obtain a preliminary assessment of the effect of a single dose of VEGF Trap-Eye on central retinal thickness (CRT) at the center point as determined by optical coherence tomography (OCT)
   Assessments for CRT are performed at each visit (Visit 1 - Visit 10) by means of OCT.
3. To obtain a preliminary assessment of the effect of a single IVT administration of VEGF Trap-Eye on visual acuity
   Assessments for visual acuity are performed at each visit (Visit 1 - Visit 10).

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosis of diabetes mellitus (type 1 or type 2).
- Best corrected E-ETDRS visual acuity score of ≥ 24 letters (i.e., 20/320 or better) and ≤ 73 letters (i.e., 20/40 or worse).
- On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.
- Retinal Thickness at the center point ≥ 250 microns.
- Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Visit 2 (Day 1).
- Macular edema due to causes other than diabetic macular edema. An eye should be considered ineligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.
- An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).
- An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase 1 study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Maryland**

Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte, North Carolina, United States, 28210

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320814

Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Latest version (submitted June 8, 2011) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	○	○	September 6, 2006	Recruitment Status, Study Status and Contacts/Locations
3	◉	◉	January 5, 2009	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Oversight, Contacts/Locations, Study Design and Sponsor/Collaborators

Version	A	B	Submitted Date	Changes
4	○	○	January 25, 2011	Study Status
5	○	○	June 8, 2011	Study Status

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320814

Submitted Date: January 5, 2009 (v3)

Study Identification

Unique Protocol ID: VGFT-OD-0512

Brief Title: Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients With Diabetic Macular Edema

Secondary IDs:

Study Status

Record Verification: January 2009

Overall Status: Completed

Study Start: April 2006

Primary Completion: August 2006 [Actual]

Study Completion: August 2007 [Actual]

First Submitted: April 28, 2006

First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	January 5, 2009
Last Update Posted:	January 6, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with diabetic macular edema.
Detailed Description:	This is an open label study. Initially, 5 patients with DME will receive an ITV injection of VEGF Trap into the study eye. Additional patients may be enrolled at the same or additional dose levels. Patients will be observed for six weeks following the injection for assessments of ocular and systemic safety.

Conditions

Conditions:	Diabetic Macular Edema
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase: Phase 1

Interventional Study Model: Single Group Assignment

Number of Arms: 1

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 5 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1	Drug: VEGF Trap-Eye single IVT injection of 4.0 mg of VEGF Trap-Eye into the study eye on Day 1

Outcome Measures

Primary Outcome Measures:

1. To assess the ocular and systemic safety and tolerability of a single intravitreal (IVT) injection of VEGF Trap-Eye in patients with diabetic macular edema (DME)
   Assessments for safety and tolerablity are performed at each visit (Visit 1 - Visit 10)

Secondary Outcome Measures:

2. To obtain a preliminary assessment of the effect of a single dose of VEGF Trap-Eye on central retinal thickness (CRT) at the center point as determined by optical coherence tomography (OCT)
   Assessments for CRT are performed at each visit (Visit 1 - Visit 10) by means of OCT.
3. To obtain a preliminary assessment of the effect of a single IVT administration of VEGF Trap-Eye on visual acuity
   Assessments for visual acuity are performed at each visit (Visit 1 - Visit 10).

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosis of diabetes mellitus (type 1 or type 2).
- Best corrected E-ETDRS visual acuity score of ≥ 24 letters (i.e., 20/320 or better) and ≤ 73 letters (i.e., 20/40 or worse).
- On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.
- Retinal Thickness at the center point ≥ 250 microns.
- Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Visit 2 (Day 1).
- Macular edema due to causes other than diabetic macular edema. An eye should be considered ineligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.
- An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).
- An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase 1 study.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Maryland**

Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte, North Carolina, United States, 28210

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320814

Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Latest version (submitted June 8, 2011) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	April 28, 2006	None (earliest Version on record)
2	◉	◉	September 6, 2006	Recruitment Status, Study Status and Contacts/Locations
3	○	○	January 5, 2009	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Oversight, Contacts/Locations, Study Design and Sponsor/Collaborators

Version	A	B	Submitted Date	Changes
4	○	○	January 25, 2011	Study Status
5	○	○	June 8, 2011	Study Status

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320814

Submitted Date: September 6, 2006 (v2)

Study Identification

Unique Protocol ID: VGFT-OD-0512

Brief Title: Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients With Diabetic Macular Edema

Secondary IDs:

Study Status

Record Verification: September 2006

Overall Status: Active, not recruiting

Study Start: April 2006

Primary Completion:

Study Completion:

First Submitted: April 28, 2006

First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	September 6, 2006
Last Update Posted:	September 8, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with diabetic macular edema.
Detailed Description:	This is an open label study. Initially, 5 patients with DME will receive an ITV injection of VEGF Trap into the study eye. Additional patients may be enrolled at the same or additional dose levels. Patients will be observed for six weeks following the injection for assessments of ocular and systemic safety.

Conditions

Conditions:	Diabetic Macular Edema
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase: Phase 1

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 5

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, Bioeffect

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on: central retinal thickness, visual acuity and anti-VEGF Trap antibodies in the systemic circulation

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosis of diabetes mellitus (type 1 or type 2).
- Best corrected E-ETDRS visual acuity score of ≥ 24 letters (i.e., 20/320 or better) and ≤ 73 letters (i.e., 20/40 or worse).

- On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.
- Retinal Thickness at the center point ≥ 250 microns.
- Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Visit 2 (Day 1).
- Macular edema due to causes other than diabetic macular edema. An eye should be considered ineligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.
- An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).
- An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase 1 study.

Contacts/Locations

Locations: **United States, Maryland**

Baltimore, Maryland, United States, 21287

United States, North Carolina

Charlotte, North Carolina, United States, 28210

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00320814

Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Latest version (submitted June 8, 2011) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	◉	April 28, 2006	None (earliest Version on record)
2	○	○	September 6, 2006	Recruitment Status, Study Status and Contacts/Locations
3	○	○	January 5, 2009	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Oversight, Contacts/Locations, Study Design and Sponsor/Collaborators

Version	A	B	Submitted Date	Changes
4	○	○	January 25, 2011	Study Status
5	○	○	June 8, 2011	Study Status

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00320814

Submitted Date: April 28, 2006 (v1)

Study Identification

Unique Protocol ID: VGFT-OD-0512

Brief Title: Phase 1 Study of VEGF Trap in Patients With Diabetic Macular Edema

Official Title: An Exploratory Study of the Safety, Tolerability and Biological Effect of a Single Intravitreal Administration of VEGF Trap in Patients With Diabetic Macular Edema

Secondary IDs:

Study Status

Record Verification: April 2006

Overall Status: Recruiting

Study Start: April 2006

Primary Completion:

Study Completion:

First Submitted: April 28, 2006

First Submitted that Met QC Criteria:	April 28, 2006
First Posted:	May 3, 2006 [Estimate]
Last Update Submitted that Met QC Criteria:	April 28, 2006
Last Update Posted:	May 3, 2006 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary:	To assess the ocular and systemic safety and tolerability of a single intravitreal injection of VEGF Trap in patients with diabetic macular edema.
Detailed Description:	This is an open label study. Initially, 5 patients with DME will receive an ITV injection of VEGF Trap into the study eye. Additional patients may be enrolled at the same or additional dose levels. Patients will be observed for six weeks following the injection for assessments of ocular and systemic safety.

Conditions

Conditions:	Diabetic Macular Edema
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase: Phase 1

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 5

Arms and Interventions

Intervention Details:

Drug: VEGF Trap

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability, Bioeffect

Secondary Outcome Measures:

2. The effect of VEGF Trap administration on: central retinal thickness, visual acuity and anti-VEGF Trap antibodies in the systemic circulation

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosis of diabetes mellitus (type 1 or type 2).
- Best corrected E-ETDRS visual acuity score of ≥ 24 letters (i.e., 20/320 or better) and ≤ 73 letters (i.e., 20/40 or worse).

- On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.
- Retinal Thickness at the center point ≥ 250 microns.
- Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion Criteria:

- History of any vitreous hemorrhage within 4 weeks prior to Visit 2 (Day 1).
- Macular edema due to causes other than diabetic macular edema. An eye should be considered ineligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.
- An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).
- An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).
- Presence of any other condition or laboratory abnormality, which, in the opinion of the Investigator, would interfere with the assessment of disease status/progression or jeopardize the patient's appropriate participation in this Phase 1 study.

Contacts/Locations

Central Contact: Regeneron
Email: VEGF.Trap@regeneron.com

Locations: **United States, Maryland**

[Not yet recruiting]
Baltimore, Maryland, United States, 21287

United States, North Carolina

[Recruiting]

Charlotte, North Carolina, United States, 28210

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	◉	◉	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: December 1, 2011 (v15)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2011

Overall Status: Completed

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Actual]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	December 1, 2011
Last Update Posted:	December 8, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	1217 [Actual]

Arms and Interventions

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

Arms	Assigned Interventions
Active Comparator: 4	Drug: ranibizumab 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
   Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.

15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	◉	◉	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: May 4, 2011 (v14)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: April 2011

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	May 4, 2011
Last Update Posted:	May 6, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	1217 [Actual]

Arms and Interventions

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

Arms	Assigned Interventions
Active Comparator: 4	Drug: ranibizumab 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
   Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.

15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	◉	◉	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: April 18, 2011 (v13)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: April 2011

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	April 18, 2011
Last Update Posted:	April 27, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	1217 [Actual]

Arms and Interventions

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

Arms	Assigned Interventions
Active Comparator: 4	Drug: ranibizumab 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
   Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.

15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	◉	◉	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: January 5, 2011 (v12)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: January 2011

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: December 2011 [Anticipated]

Study Completion: December 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	January 5, 2011
Last Update Posted:	January 10, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	1200 [Anticipated]

Arms and Interventions

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

Arms	Assigned Interventions
Active Comparator: 4	Drug: ranibizumab 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
   Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.

15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	◉	◉	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: December 1, 2009 (v11)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2009

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: December 2011 [Anticipated]

Study Completion: December 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	December 1, 2009
Last Update Posted:	December 2, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

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

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has

lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	◉	◉	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: September 12, 2009 (v10)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: September 2009

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: December 2011 [Anticipated]

Study Completion: December 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	September 12, 2009
Last Update Posted:	September 15, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

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

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has

lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	◉	◉	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: April 28, 2009 (v9)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: April 2009

Overall Status: Recruiting

Study Start: August 2007

Primary Completion: December 2011 [Anticipated]

Study Completion: December 2011 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	April 28, 2009
Last Update Posted:	April 29, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

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

Outcome Measures

Primary Outcome Measures:

1. The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has

lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)
Week 52

Secondary Outcome Measures:

2. Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52
   Week 52
3. The proportion of subjects who gain at least 15 letters of vision at Week 52
   Week 52
4. Mean change from baseline in total NEI VFQ-25 score at Week 52
   Week 52
5. Mean change from baseline in CNV area at Week 52
   Week 52

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Recruiting]
Birmingham, Alabama, United States, 35205

[Recruiting]
Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]
Phoenix, Arizona, United States, 85014

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]
Tucson, Arizona, United States, 85704

[Recruiting]
Tucson, Arizona, United States, 85710

United States, California

[Recruiting]
Beverly Hills, California, United States, 90211

[Recruiting]
Campbell, California, United States, 95008

[Recruiting]
Fullerton, California, United States, 92835

[Terminated]
Glendale, California, United States, 91203

[Recruiting]
Irvine, California, United States, 92697

[Recruiting]
La Jolla, California, United States, 92037

[Recruiting]

Loma Linda, California, United States, 92354

[Withdrawn]

Los Angeles, California, United States, 90033

[Recruiting]

Los Angeles, California, United States, 90048

[Recruiting]

Menlo Park, California, United States, 94025

[Recruiting]

Mountain View, California, United States, 94040

[Recruiting]

Oakland, California, United States, 94609

[Recruiting]

Palm Springs, California, United States, 92262

[Recruiting]

Pasadena, California, United States, 91105

[Withdrawn]

Poway, California, United States, 92064

[Recruiting]

Sacramento, California, United States, 95819

[Active, not recruiting]

San Diego, California, United States, 92120

[Terminated]

San Francisco, California, United States, 94107

[Recruiting]

Santa Ana, California, United States, 92705

[Recruiting]

Torrance, California, United States, 90503

[Withdrawn]

Ventura, California, United States, 93003

[Recruiting]

Westlake Village, California, United States, 91361

[Recruiting]

Yorba Linda, California, United States, 92887

United States, Colorado

[Terminated]

Aurora, Colorado, United States, 80045

[Recruiting]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80230

United States, Connecticut

[Recruiting]

Bridgeport, Connecticut, United States, 06606

[Withdrawn]

Hamden, Connecticut, United States, 06518

[Active, not recruiting]

New Haven, Connecticut, United States, 06510

[Recruiting]

New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Fort Myers, Florida, United States, 33907

[Withdrawn]

Ft. Lauderdale, Florida, United States, 33351

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Withdrawn]

Gainesville, Florida, United States, 32610

[Recruiting]

Jacksonville, Florida, United States, 32224

[Withdrawn]

Miami, Florida, United States, 33136

[Recruiting]

Miami, Florida, United States, 33143

[Terminated]

Mount Dora, Florida, United States, 32757

[Recruiting]

Orlando, Florida, United States, 32803

[Recruiting]

Orlando, Florida, United States, 32806

[Recruiting]

Oscala, Florida, United States, 34472

[Recruiting]

Palm Beach Gardens, Florida, United States, 33410

[Recruiting]

Pensacola, Florida, United States, 32503

[Withdrawn]

Sarasota, Florida, United States

[Recruiting]

Stuart, Florida, United States, 34994

[Recruiting]

Tampa, Florida, United States, 33612

[Recruiting]

Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]

Augusta, Georgia, United States, 30909

United States, Hawaii

[Recruiting]

Aiea, Hawaii, United States, 96701

[Withdrawn]

Honolulu, Hawaii, United States, 96813

United States, Illinois

[Recruiting]

Oak Brook, Illinois, United States, 60523

United States, Indiana

[Recruiting]

Fort Wayne, Indiana, United States, 46804

[Recruiting]

Indianapolis, Indiana, United States, 46202

[Terminated]

Indianapolis, Indiana, United States, 46260

[Recruiting]

Indianapolis, Indiana, United States, 46280

[Recruiting]

New Albany, Indiana, United States, 47150

United States, Iowa

[Recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]
Wichita, Kansas, United States, 67214

United States, Kentucky

[Recruiting]
Louisville, Kentucky, United States, 40202

[Recruiting]
Louisville, Kentucky, United States, 40207

[Terminated]
Paducah, Kentucky, United States, 42001

United States, Louisiana

[Recruiting]
New Orleans, Louisiana, United States, 70115

[Recruiting]
New Orleans, Louisiana, United States, 70121

[Terminated]
Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]
Bangor, Maine, United States, 04401

[Recruiting]
Portland, Maine, United States, 04102

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Withdrawn]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Recruiting]

Boston, Massachusetts, United States, 02215

[Withdrawn]

Boston, Massachusetts, United States

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Recruiting]

Ann Arbor, Michigan, United States, 48105

[Recruiting]

Battle Creek, Michigan, United States, 49015

[Active, not recruiting]

Detroit, Michigan, United States, 48202

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Withdrawn]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Withdrawn]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Withdrawn]

Kansas City, Missouri, United States, 64111

[Recruiting]

Springfield, Missouri, United States, 65804

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]

Lincoln, Nebraska, United States, 68506

[Withdrawn]

Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]

Las Vegas, Nevada, United States, 89144

United States, New Jersey

[Recruiting]

Lawrenceville, New Jersey, United States, 08648

[Terminated]

New Brunswick, New Jersey, United States, 08901

[Recruiting]

Northfield, New Jersey, United States, 08225

[Withdrawn]

Teaneck, New Jersey, United States, 07666

[Recruiting]

Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Recruiting]

Albany, New York, United States, 12206

[Recruiting]

Brooklyn, New York, United States, 11223

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Recruiting]

New York, New York, United States, 10032

[Terminated]

Poughkeepsie, New York, United States, 12601

[Recruiting]

Rochester, New York, United States, 14620

[Recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

[Recruiting]

Syracuse, New York, United States, 13224

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Recruiting]

Raleigh, North Carolina, United States, 27607

[Terminated]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

[Withdrawn]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Terminated]

Columbus, Ohio, United States, 43215

[Terminated]

Toledo, Ohio, United States, 43608

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Recruiting]

Ashland, Oregon, United States, 97520

[Recruiting]

Portland, Oregon, United States, 97210

[Recruiting]

Portland, Oregon, United States, 97227

[Recruiting]

Salem, Oregon, United States, 97302

United States, Pennsylvania

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Active, not recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsberg, Pennsylvania, United States, 15231

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Recruiting]

West Mifflin, Pennsylvania, United States, 15122

[Withdrawn]

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Charleston, South Carolina, United States, 29414

[Recruiting]

Columbia, South Carolina, United States, 29223

[Recruiting]

Greenville, South Carolina, United States, 29605

[Recruiting]

West Columbia, South Carolina, United States, 29169

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Terminated]

Memphis, Tennessee, United States, 38119

[Terminated]

Memphis, Tennessee, United States, 38120

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Abilene, Texas, United States, 79606

[Recruiting]

Austin, Texas, United States, 78705

[Active, not recruiting]

Corpus Cristi, Texas, United States, 78413

[Recruiting]

Dallas, Texas, United States, 75390

[Terminated]

DeSoto, Texas, United States, 75115

[Recruiting]

Ft. Worth, Texas, United States, 76102

[Recruiting]

Ft. Worth, Texas, United States, 76104

[Withdrawn]

Galveston, Texas, United States, 77555

[Recruiting]

Houston, Texas, United States, 77030

[Withdrawn]

Houston, Texas, United States, 77030

[Terminated]

Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Fairfax, Virginia, United States, 22031

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Recruiting]

Silverdale, Washington, United States, 98383

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53715

[Recruiting]

Madison, Wisconsin, United States, 58705

[Recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Recruiting]

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

[Recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Recruiting]

London, Ontario, Canada, N6A 4G5

[Recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Recruiting]

Ottawa, Ontario, Canada, K1H8L6

[Recruiting]

Toronto, Ontario, Canada, M4N3M5

[Active, not recruiting]

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

[Recruiting]

Montreal, Quebec, Canada, H1T 2M4

[Recruiting]

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Recruiting]

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	◉	◉	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: March 3, 2009 (v8)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: March 2009

Overall Status: Recruiting

Study Start: August 2007

Primary Completion: October 2010 [Anticipated]

Study Completion: January 2012 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	March 3, 2009
Last Update Posted:	March 5, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab

Arms	Assigned Interventions
Experimental: 2	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab

Arms	Assigned Interventions
Experimental: 3	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab
Active Comparator: 4	Drug: Comparator 0.5 mg ranibizumab adm. every 4 wks (RQ4);

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline.
   Monthly

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.
   as dictated by protocol

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. CNV must be at least 50% of total lesion size.
5. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
6. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Prior treatment with anti-VEGF agents as follows:
    - Prior treatment with anti-VEGF therapy in the study eye is not allowed.
    - Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye is allowed.

- Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study

4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Recruiting]

Birmingham, Alabama, United States, 35205

[Recruiting]

Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]

Phoenix, Arizona, United States, 85014

[Recruiting]

Phoenix, Arizona, United States, 85020

[Recruiting]

Tucson, Arizona, United States, 85704

[Recruiting]

Tucson, Arizona, United States, 85710

United States, California

[Recruiting]

Beverly Hills, California, United States, 90211

[Recruiting]

Campbell, California, United States, 95008

[Recruiting]

Fullerton, California, United States, 92835

[Terminated]

Glendale, California, United States, 91203

[Recruiting]

Irvine, California, United States, 92697

[Recruiting]

La Jolla, California, United States, 92037

[Recruiting]

Loma Linda, California, United States, 92354

[Withdrawn]

Los Angeles, California, United States, 90033

[Recruiting]

Los Angeles, California, United States, 90048

[Recruiting]

Menlo Park, California, United States, 94025

[Recruiting]

Mountain View, California, United States, 94040

[Recruiting]

Oakland, California, United States, 94609

[Recruiting]

Palm Springs, California, United States, 92262

[Recruiting]

Pasadena, California, United States, 91105

[Withdrawn]

Poway, California, United States, 92064

[Recruiting]

Sacramento, California, United States, 95819

[Active, not recruiting]

San Diego, California, United States, 92120

[Terminated]

San Francisco, California, United States, 94107

[Recruiting]

Santa Ana, California, United States, 92705

[Recruiting]

Torrance, California, United States, 90503

[Withdrawn]

Ventura, California, United States, 93003

[Recruiting]

Westlake Village, California, United States, 91361

[Recruiting]

Yorba Linda, California, United States, 92887

United States, Colorado

[Terminated]

Aurora, Colorado, United States, 80045

[Recruiting]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80230

United States, Connecticut

[Recruiting]

Bridgeport, Connecticut, United States, 06606

[Withdrawn]

Hamden, Connecticut, United States, 06518

[Active, not recruiting]

New Haven, Connecticut, United States, 06510

[Recruiting]

New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Fort Myers, Florida, United States, 33907

[Withdrawn]

Ft. Lauderdale, Florida, United States, 33351

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Withdrawn]

Gainesville, Florida, United States, 32610

[Recruiting]

Jacksonville, Florida, United States, 32224

[Withdrawn]

Miami, Florida, United States, 33136

[Recruiting]

Miami, Florida, United States, 33143

[Terminated]

Mount Dora, Florida, United States, 32757

[Recruiting]

Orlando, Florida, United States, 32803

[Recruiting]

Orlando, Florida, United States, 32806

[Recruiting]

Oscala, Florida, United States, 34472

[Recruiting]

Palm Beach Gardens, Florida, United States, 33410

[Recruiting]

Pensacola, Florida, United States, 32503

[Withdrawn]

Sarasota, Florida, United States

[Recruiting]

Stuart, Florida, United States, 34994

[Recruiting]

Tampa, Florida, United States, 33612

[Recruiting]

Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]

Augusta, Georgia, United States, 30909

United States, Hawaii

[Recruiting]

Aiea, Hawaii, United States, 96701

[Withdrawn]

Honolulu, Hawaii, United States, 96813

United States, Illinois

[Recruiting]

Oak Brook, Illinois, United States, 60523

United States, Indiana

[Recruiting]

Fort Wayne, Indiana, United States, 46804

[Recruiting]

Indianapolis, Indiana, United States, 46202

[Terminated]

Indianapolis, Indiana, United States, 46260

[Recruiting]

Indianapolis, Indiana, United States, 46280

[Recruiting]

New Albany, Indiana, United States, 47150

United States, Iowa

[Recruiting]

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]

Wichita, Kansas, United States, 67214

United States, Kentucky

[Recruiting]

Louisville, Kentucky, United States, 40202

[Recruiting]

Louisville, Kentucky, United States, 40207

[Terminated]

Paducah, Kentucky, United States, 42001

United States, Louisiana

[Recruiting]

New Orleans, Louisiana, United States, 70115

[Recruiting]

New Orleans, Louisiana, United States, 70121

[Terminated]

Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]

Bangor, Maine, United States, 04401

[Recruiting]

Portland, Maine, United States, 04102

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Withdrawn]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Recruiting]

Boston, Massachusetts, United States, 02215

[Withdrawn]

Boston, Massachusetts, United States

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Recruiting]

Ann Arbor, Michigan, United States, 48105

[Recruiting]

Battle Creek, Michigan, United States, 49015

[Active, not recruiting]

Detroit, Michigan, United States, 48202

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Withdrawn]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Withdrawn]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Withdrawn]

Kansas City, Missouri, United States, 64111

[Recruiting]

Springfield, Missouri, United States, 65804

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]

Lincoln, Nebraska, United States, 68506

[Withdrawn]

Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]

Las Vegas, Nevada, United States, 89144

United States, New Jersey

[Recruiting]

Lawrenceville, New Jersey, United States, 08648

[Terminated]

New Brunswick, New Jersey, United States, 08901

[Recruiting]

Northfield, New Jersey, United States, 08225

[Withdrawn]

Teaneck, New Jersey, United States, 07666

[Recruiting]

Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Recruiting]

Albany, New York, United States, 12206

[Recruiting]

Brooklyn, New York, United States, 11223

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Recruiting]

New York, New York, United States, 10032

[Terminated]

Poughkeepsie, New York, United States, 12601

[Recruiting]

Rochester, New York, United States, 14620

[Recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

[Recruiting]

Syracuse, New York, United States, 13224

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Recruiting]

Raleigh, North Carolina, United States, 27607

[Terminated]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

[Withdrawn]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Terminated]

Columbus, Ohio, United States, 43215

[Terminated]

Toledo, Ohio, United States, 43608

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Recruiting]

Ashland, Oregon, United States, 97520

[Recruiting]

Portland, Oregon, United States, 97210

[Recruiting]

Portland, Oregon, United States, 97227

[Recruiting]

Salem, Oregon, United States, 97302

United States, Pennsylvania

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Active, not recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsberg, Pennsylvania, United States, 15231

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Recruiting]

West Mifflin, Pennsylvania, United States, 15122

[Withdrawn]

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Charleston, South Carolina, United States, 29414

[Recruiting]

Columbia, South Carolina, United States, 29223

[Recruiting]

Greenville, South Carolina, United States, 29605

[Recruiting]

West Columbia, South Carolina, United States, 29169

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Terminated]

Memphis, Tennessee, United States, 38119

[Terminated]

Memphis, Tennessee, United States, 38120

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Abilene, Texas, United States, 79606

[Recruiting]

Austin, Texas, United States, 78705

[Active, not recruiting]

Corpus Cristi, Texas, United States, 78413

[Recruiting]

Dallas, Texas, United States, 75390

[Terminated]

DeSoto, Texas, United States, 75115

[Recruiting]

Ft. Worth, Texas, United States, 76102

[Recruiting]

Ft. Worth, Texas, United States, 76104

[Withdrawn]

Galveston, Texas, United States, 77555

[Recruiting]

Houston, Texas, United States, 77030

[Withdrawn]

Houston, Texas, United States, 77030

[Terminated]

Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Fairfax, Virginia, United States, 22031

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Recruiting]

Silverdale, Washington, United States, 98383

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53715

[Recruiting]

Madison, Wisconsin, United States, 58705

[Recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Recruiting]

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

[Recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Recruiting]

London, Ontario, Canada, N6A 4G5

[Recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Recruiting]

Ottawa, Ontario, Canada, K1H8L6

[Recruiting]

Toronto, Ontario, Canada, M4N3M5

[Active, not recruiting]

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

[Recruiting]

Montreal, Quebec, Canada, H1T 2M4

[Recruiting]

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Recruiting]

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	◉	◉	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: January 22, 2009 (v7)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: January 2009

Overall Status: Recruiting

Study Start: August 2007

Primary Completion: October 2010 [Anticipated]

Study Completion: January 2012 [Anticipated]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	January 22, 2009
Last Update Posted:	January 26, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab

Arms	Assigned Interventions
Experimental: 2	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab

Arms	Assigned Interventions
Experimental: 3	Drug: VEGF Trap-Eye VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be rand. assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:1)2mg VEGF Trap-Eye adm. every 4 wks (2Q4), 2) 0.5mg VEGF Trap-Eye adm. every 4 wks (0.5Q4), 3) 2mg VEGF Trap-Eye adm. every 8 wks (2Q8), and 4) 0.5mg ranibizumab adm. every 4 wks (RQ4); subj. assigned to (2Q8) will receive the 2mg injection every 4 wks to wk 8 & then a sham inject at interim 4-wk visits (when study drug is not to be adm) during the first 52 wks of the study. VEGF Trap-Eye will be supplied in sealed 3mL single use vials each with a "withdrawable" vol. of approx. 0.5 mL at a concentration of 10mg/mL or 40 mg/mL.VEGF Trap-Eye will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV inject. The inject. vol. will be 50µL (0.05 mL) for the 0.5mg & 2mg doses of VEGF Trap-Eye and 0.5 mg ranibizumab
Active Comparator: 4	Drug: Comparator 0.5 mg ranibizumab adm. every 4 wks (RQ4);

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline.
   Monthly

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.
   as dictated by protocol

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. CNV must be at least 50% of total lesion size.
5. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
6. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Prior treatment with anti-VEGF agents as follows:
    - Prior treatment with anti-VEGF therapy in the study eye is not allowed.
    - Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye is allowed.

- Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study

4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Recruiting]

Birmingham, Alabama, United States, 35205

[Recruiting]

Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]

Phoenix, Arizona, United States, 85014

[Recruiting]

Phoenix, Arizona, United States, 85020

[Recruiting]

Tucson, Arizona, United States, 85704

[Recruiting]

Tucson, Arizona, United States, 85710

United States, California

[Recruiting]

Beverly Hills, California, United States, 90211

[Recruiting]

Campbell, California, United States, 95008

[Recruiting]

Fullerton, California, United States, 92835

[Terminated]

Glendale, California, United States, 91203

[Recruiting]

Irvine, California, United States, 92697

[Recruiting]

La Jolla, California, United States, 92037

[Recruiting]

Loma Linda, California, United States, 92354

[Withdrawn]

Los Angeles, California, United States, 90033

[Recruiting]

Los Angeles, California, United States, 90048

[Recruiting]

Menlo Park, California, United States, 94025

[Recruiting]

Mountain View, California, United States, 94040

[Recruiting]

Oakland, California, United States, 94609

[Recruiting]

Palm Springs, California, United States, 92262

[Recruiting]

Pasadena, California, United States, 91105

[Withdrawn]

Poway, California, United States, 92064

[Recruiting]

Sacramento, California, United States, 95819

[Active, not recruiting]

San Diego, California, United States, 92120

[Terminated]

San Francisco, California, United States, 94107

[Recruiting]

Santa Ana, California, United States, 92705

[Active, not recruiting]

Torrance, California, United States, 90503

[Withdrawn]

Ventura, California, United States, 93003

[Recruiting]

Westlake Village, California, United States, 91361

[Recruiting]

Yorba Linda, California, United States, 92887

United States, Colorado

[Terminated]

Aurora, Colorado, United States, 80045

[Recruiting]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80205

[Withdrawn]

Denver, Colorado, United States, 80230

United States, Connecticut

[Recruiting]

Bridgeport, Connecticut, United States, 06606

[Withdrawn]

Hamden, Connecticut, United States, 06518

[Active, not recruiting]

New Haven, Connecticut, United States, 06510

[Recruiting]

New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Fort Myers, Florida, United States, 33907

[Withdrawn]

Ft. Lauderdale, Florida, United States, 33351

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Withdrawn]

Gainesville, Florida, United States, 32610

[Recruiting]

Jacksonville, Florida, United States, 32224

[Withdrawn]

Miami, Florida, United States, 33136

[Recruiting]

Miami, Florida, United States, 33143

[Recruiting]

Mount Dora, Florida, United States, 32757

[Recruiting]

Orlando, Florida, United States, 32803

[Recruiting]

Orlando, Florida, United States, 32806

[Recruiting]

Oscala, Florida, United States, 34472

[Recruiting]

Palm Beach Gardens, Florida, United States, 33410

[Recruiting]

Pensacola, Florida, United States, 32503

[Withdrawn]

Sarasota, Florida, United States

[Recruiting]

Stuart, Florida, United States, 34994

[Recruiting]

Tampa, Florida, United States, 33612

[Recruiting]

Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]

Augusta, Georgia, United States, 30909

United States, Hawaii

[Recruiting]

Aiea, Hawaii, United States, 96701

[Withdrawn]

Honolulu, Hawaii, United States, 96813

United States, Illinois

[Recruiting]

Oak Brook, Illinois, United States, 60523

United States, Indiana

[Recruiting]

Fort Wayne, Indiana, United States, 46804

[Recruiting]

Indianapolis, Indiana, United States, 46202

[Terminated]

Indianapolis, Indiana, United States, 46260

[Recruiting]

Indianapolis, Indiana, United States, 46280

[Recruiting]

New Albany, Indiana, United States, 47150

United States, Iowa

[Recruiting]

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]

Wichita, Kansas, United States, 67214

United States, Kentucky

[Recruiting]

Louisville, Kentucky, United States, 40202

[Recruiting]

Louisville, Kentucky, United States, 40207

[Terminated]

Paducah, Kentucky, United States, 42001

United States, Louisiana

[Recruiting]

New Orleans, Louisiana, United States, 70115

[Recruiting]

New Orleans, Louisiana, United States, 70121

[Terminated]

Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]

Bangor, Maine, United States, 04401

[Recruiting]

Portland, Maine, United States, 04102

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Withdrawn]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Recruiting]

Boston, Massachusetts, United States, 02215

[Withdrawn]

Boston, Massachusetts, United States

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Recruiting]

Ann Arbor, Michigan, United States, 48105

[Recruiting]

Battle Creek, Michigan, United States, 49015

[Active, not recruiting]

Detroit, Michigan, United States, 48202

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Withdrawn]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Withdrawn]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Withdrawn]

Kansas City, Missouri, United States, 64111

[Recruiting]

Springfield, Missouri, United States, 65804

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]

Lincoln, Nebraska, United States, 68506

[Withdrawn]

Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]

Las Vegas, Nevada, United States, 89144

United States, New Jersey

[Recruiting]

Lawrenceville, New Jersey, United States, 08648

[Terminated]

New Brunswick, New Jersey, United States, 08901

[Recruiting]

Northfield, New Jersey, United States, 08225

[Withdrawn]

Teaneck, New Jersey, United States, 07666

[Recruiting]

Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Recruiting]

Albany, New York, United States, 12206

[Recruiting]

Brooklyn, New York, United States, 11223

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Recruiting]

New York, New York, United States, 10032

[Terminated]

Poughkeepsie, New York, United States, 12601

[Recruiting]

Rochester, New York, United States, 14620

[Recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

[Recruiting]

Syracuse, New York, United States, 13224

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Recruiting]

Raleigh, North Carolina, United States, 27607

[Terminated]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

[Withdrawn]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Terminated]

Columbus, Ohio, United States, 43215

[Recruiting]

Toledo, Ohio, United States, 43608

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Recruiting]

Ashland, Oregon, United States, 97520

[Recruiting]

Portland, Oregon, United States, 97210

[Recruiting]

Portland, Oregon, United States, 97227

[Recruiting]

Salem, Oregon, United States, 97302

United States, Pennsylvania

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Active, not recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsberg, Pennsylvania, United States, 15231

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Recruiting]

West Mifflin, Pennsylvania, United States, 15122

[Withdrawn]

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Charleston, South Carolina, United States, 29414

[Recruiting]

Columbia, South Carolina, United States, 29223

[Recruiting]

Greenville, South Carolina, United States, 29605

[Recruiting]

West Columbia, South Carolina, United States, 29169

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]

Memphis, Tennessee, United States, 38119

[Terminated]

Memphis, Tennessee, United States, 38120

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Abilene, Texas, United States, 79606

[Recruiting]

Austin, Texas, United States, 78705

[Active, not recruiting]

Corpus Cristi, Texas, United States, 78413

[Recruiting]

Dallas, Texas, United States, 75390

[Terminated]

DeSoto, Texas, United States, 75115

[Recruiting]

Ft. Worth, Texas, United States, 76102

[Recruiting]

Ft. Worth, Texas, United States, 76104

[Withdrawn]

Galveston, Texas, United States, 77555

[Recruiting]

Houston, Texas, United States, 77030

[Withdrawn]

Houston, Texas, United States, 77030

[Terminated]

Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Fairfax, Virginia, United States, 22031

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Recruiting]

Silverdale, Washington, United States, 98383

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53715

[Recruiting]

Madison, Wisconsin, United States, 58705

[Recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Recruiting]

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

[Recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Recruiting]

London, Ontario, Canada, N6A 4G5

[Recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Recruiting]

Ottawa, Ontario, Canada, K1H8L6

[Active, not recruiting]
Toronto, Ontario, Canada, M4N3M5

[Active, not recruiting]
Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

[Recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	◉	◉	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: June 26, 2008 (v6)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: June 2008

Overall Status: Recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	June 26, 2008
Last Update Posted:	June 30, 2008 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Biological: VEGF Trap-Eye
Experimental: 2	Biological: VEGF Trap-Eye
Experimental: 3	Biological: VEGF Trap-Eye
Active Comparator: 4	Drug: Comparator

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline.

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.

3. Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. CNV must be at least 50% of total lesion size.
5. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
6. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Prior treatment with anti-VEGF agents as follows:
    - Prior treatment with anti-VEGF therapy in the study eye is not allowed.
    - Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye is allowed.
    - Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.

10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Recruiting]
Birmingham, Alabama, United States, 35205

[Recruiting]
Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]
Phoenix, Arizona, United States, 85014

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]

Tucson, Arizona, United States, 85704

[Recruiting]

Tucson, Arizona, United States, 85710

United States, California

[Recruiting]

Beverly Hills, California, United States, 90211

[Recruiting]

Campbell, California, United States, 95008

[Recruiting]

Fullerton, California, United States, 92835

[Not yet recruiting]

Glendale, California, United States, 91203

[Recruiting]

Irvine, California, United States, 92697

[Recruiting]

La Jolla, California, United States, 92037

[Recruiting]

Loma Linda, California, United States, 92354

[Not yet recruiting]

Los Angeles, California, United States, 90033

[Not yet recruiting]

Los Angeles, California, United States, 90048

[Recruiting]

Menlo Park, California, United States, 94025

[Recruiting]

Mountain View, California, United States, 94040

[Recruiting]

Oakland, California, United States, 94609

[Recruiting]

Orange, California, United States, 92868

[Recruiting]

Palm Springs, California, United States, 92262

[Recruiting]

Pasadena, California, United States, 91105

[Not yet recruiting]

Poway, California, United States, 92064

[Recruiting]

Sacramento, California, United States, 95819

[Not yet recruiting]

San Diego, California, United States, 92120

[Recruiting]

San Francisco, California, United States, 94107

[Recruiting]

Santa Ana, California, United States, 92705

[Not yet recruiting]

Ventura, California, United States, 93003

[Recruiting]

Westlake Village, California, United States, 91361

[Not yet recruiting]

Yorba Linda, California, United States, 92887

United States, Colorado

[Recruiting]

Aurora, Colorado, United States, 80045

[Recruiting]

Denver, Colorado, United States, 80205

United States, Connecticut

[Recruiting]

Bridgeport, Connecticut, United States, 06606

[Not yet recruiting]

New Haven, Connecticut, United States, 06510

[Recruiting]

New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Fort Myers, Florida, United States, 33907

[Not yet recruiting]

Ft. Lauderdale, Florida, United States, 33351

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Not yet recruiting]

Gainesville, Florida, United States, 32610

[Recruiting]

Jacksonville, Florida, United States, 32224

[Not yet recruiting]

Miami, Florida, United States, 33136

[Not yet recruiting]

Miami, Florida, United States, 33143

[Not yet recruiting]

Mount Dora, Florida, United States, 32757

[Recruiting]

Orlando, Florida, United States, 32803

[Recruiting]

Orlando, Florida, United States, 32806

[Recruiting]

Oscala, Florida, United States, 34472

[Recruiting]

Palm Beach Gardens, Florida, United States, 33410

[Recruiting]

Pensacola, Florida, United States, 32503

[Recruiting]

Stuart, Florida, United States, 34994

[Recruiting]

Tampa, Florida, United States, 33612

[Recruiting]

Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]

Augusta, Georgia, United States, 30909

United States, Hawaii

[Recruiting]

Aiea, Hawaii, United States, 96701

United States, Illinois

[Suspended]

Chicago, Illinois, United States, 60637

[Recruiting]

Glenview, Illinois, United States, 90026

[Recruiting]

Oak Brook, Illinois, United States, 60523

United States, Indiana

[Recruiting]
Fort Wayne, Indiana, United States, 46804

[Recruiting]
Indianapolis, Indiana, United States, 46202

[Recruiting]
Indianapolis, Indiana, United States, 46260

[Recruiting]
Indianapolis, Indiana, United States, 46280

[Recruiting]
New Albany, Indiana, United States, 47150

United States, Iowa

[Recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]
Wichita, Kansas, United States, 67214

United States, Kentucky

[Recruiting]
Louisville, Kentucky, United States, 40202

[Recruiting]
Louisville, Kentucky, United States, 40207

[Recruiting]
Paducah, Kentucky, United States, 42001

United States, Louisiana

[Recruiting]
New Orleans, Louisiana, United States, 70115

[Recruiting]

New Orleans, Louisiana, United States, 70121

[Recruiting]

Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]

Bangor, Maine, United States, 04401

[Recruiting]

Portland, Maine, United States, 04102

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Not yet recruiting]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Not yet recruiting]

Boston, Massachusetts, United States, 02215

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Recruiting]
Ann Arbor, Michigan, United States, 48105

[Recruiting]
Battle Creek, Michigan, United States, 49015

[Not yet recruiting]
Detroit, Michigan, United States, 48202

[Recruiting]
Grand Rapids, Michigan, United States, 49525

[Recruiting]
Jackson, Michigan, United States, 49201

[Recruiting]
Royal Oak, Michigan, United States, 48073

[Recruiting]
Southfield, Michigan, United States, 48034

United States, Minnesota

[Recruiting]
Minneapolis, Minnesota, United States, 55404

[Recruiting]
Rochester, Minnesota, United States, 55905

United States, Missouri

[Recruiting]
Florissant, Missouri, United States, 63031

[Recruiting]
Kansas City, Missouri, United States, 64108

[Recruiting]
Springfield, Missouri, United States, 65804

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]

Lincoln, Nebraska, United States, 68506

United States, Nevada

[Recruiting]

Las Vegas, Nevada, United States, 89144

United States, New Jersey

[Recruiting]

Lawrenceville, New Jersey, United States, 08648

[Recruiting]

New Brunswick, New Jersey, United States, 08901

[Recruiting]

Northfield, New Jersey, United States, 08225

[Recruiting]

Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Recruiting]

Albany, New York, United States, 12159

[Recruiting]

Albany, New York, United States, 12206

[Recruiting]

Brooklyn, New York, United States, 11223

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Recruiting]

New York, New York, United States, 10032

[Recruiting]

Poughkeepsie, New York, United States, 12601

[Recruiting]

Rochester, New York, United States, 14620

[Recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Recruiting]

Raleigh, North Carolina, United States, 27607

[Recruiting]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

[Not yet recruiting]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Recruiting]

Columbus, Ohio, United States, 43215

[Recruiting]

Toledo, Ohio, United States, 43608

United States, Oklahoma

[Recruiting]

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

[Not yet recruiting]

Ashland, Oregon, United States, 97520

[Recruiting]

Portland, Oregon, United States, 97210

[Recruiting]

Portland, Oregon, United States, 97227

[Recruiting]

Salem, Oregon, United States, 97302

United States, Pennsylvania

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Not yet recruiting]

Pittsburgh, Pennsylvania, United States, 15219

[Recruiting]

West Mifflin, Pennsylvania, United States, 15122

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Not yet recruiting]

Charleston, South Carolina, United States, 29414

[Recruiting]

Columbia, South Carolina, United States, 29223

[Recruiting]

Greenville, South Carolina, United States, 29605

[Not yet recruiting]

Mt. Pleasant, South Carolina, United States, 29464

[Recruiting]

West Columbia, South Carolina, United States, 29169

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]

Memphis, Tennessee, United States, 38119

[Terminated]

Memphis, Tennessee, United States, 38120

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Abilene, Texas, United States, 79606

[Recruiting]

Austin, Texas, United States, 78705

[Not yet recruiting]

Corpus Christi, Texas, United States, 78413

[Not yet recruiting]

Dallas, Texas, United States, 75390

[Recruiting]

DeSoto, Texas, United States, 75115

[Recruiting]

Ft. Worth, Texas, United States, 76102

[Recruiting]

Ft. Worth, Texas, United States, 76104

[Not yet recruiting]

Galveston, Texas, United States, 77555

[Recruiting]

Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Fairfax, Virginia, United States, 22031

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Recruiting]

Silverdale, Washington, United States, 98383

United States, Wisconsin

[Recruiting]

Madison, Wisconsin, United States, 53715

[Recruiting]

Madison, Wisconsin, United States, 58705

[Recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Recruiting]

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

[Not yet recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Recruiting]

London, Ontario, Canada, N6A 4G5

[Recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Not yet recruiting]

Ottawa, Ontario, Canada, K1H8L6

[Not yet recruiting]

Toronto, Ontario, Canada, M4N3M5

[Not yet recruiting]

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

[Recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1562 of 2000

U.S. National Library of Medicine

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)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	◉	◉	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: March 13, 2008 (v5)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: March 2008

Overall Status: Recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	March 13, 2008
Last Update Posted:	March 17, 2008 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap-Eye

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. CNV must be at least 50% of total lesion size.
5. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
6. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.

7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Prior treatment with anti-VEGF agents as follows:
    - Prior treatment with anti-VEGF therapy in the study eye is not allowed.
    - Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye is allowed.
    - Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.

14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Not yet recruiting]
Birmingham, Alabama, United States, 35205

[Not yet recruiting]
Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]
Phoenix, Arizona, United States, 85014

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]
Tucson, Arizona, United States, 85704

[Not yet recruiting]
Tucson, Arizona, United States, 85710

[Not yet recruiting]
Tucson, Arizona, United States, 85711

United States, California

[Recruiting]
Beverly Hills, California, United States, 90211

[Not yet recruiting]
Fullerton, California, United States, 92835

[Not yet recruiting]
Glendale, California, United States, 91203

[Not yet recruiting]
Irvine, California, United States, 92697

[Not yet recruiting]
La Jolla, California, United States, 92037

[Recruiting]
Loma Linda, California, United States, 92354

[Not yet recruiting]
Los Angeles, California, United States, 90033

[Not yet recruiting]
Los Angeles, California, United States, 90048

[Not yet recruiting]
Menlo Park, California, United States, 94025

[Recruiting]
Mountain View, California, United States, 94040

[Recruiting]
Oakland, California, United States, 94609

[Recruiting]
Palm Springs, California, United States, 92262

[Recruiting]
Pasadena, California, United States, 91105

[Not yet recruiting]
Poway, California, United States, 92064

[Not yet recruiting]
Sacramento, California, United States, 95819

[Not yet recruiting]
San Diego, California, United States, 92120

[Recruiting]
San Francisco, California, United States, 94107

[Not yet recruiting]
San Marino, California, United States, 91108

[Recruiting]
Santa Ana, California, United States, 92705

[Not yet recruiting]
Ventura, California, United States, 93003

[Recruiting]
Westlake Village, California, United States, 91361

[Not yet recruiting]
Yorba Linda, California, United States, 92887

United States, Colorado

[Not yet recruiting]
Aurora, Colorado, United States, 80045

[Not yet recruiting]
Denver, Colorado, United States, 80205

[Not yet recruiting]
Denver, Colorado, United States, 80230

United States, Connecticut

[Not yet recruiting]
Bridgeport, Connecticut, United States, 06606

[Recruiting]
Hamden, Connecticut, United States, 06518

[Not yet recruiting]

New Haven, Connecticut, United States, 06520

[Recruiting]

New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Delray Beach, Florida, United States, 33484

[Recruiting]

Fort Myers, Florida, United States, 33907

[Not yet recruiting]

Ft. Lauderdale, Florida, United States, 33334

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Not yet recruiting]

Gainesville, Florida, United States, 32610

[Not yet recruiting]

Jacksonville, Florida, United States, 32216

[Not yet recruiting]

Jacksonville, Florida, United States, 32224

[Not yet recruiting]

Margate, Florida, United States, 33063

[Not yet recruiting]

Miami, Florida, United States, 33125

[Not yet recruiting]

Miami, Florida, United States, 33136

[Not yet recruiting]
Mount Dora, Florida, United States, 32757

[Not yet recruiting]
Ocala, Florida, United States, 34472

[Recruiting]
Orlando, Florida, United States, 32806

[Recruiting]
Orlando, Florida, United States, 38203

[Recruiting]
Palm Beach Gardens, Florida, United States, 33410

[Recruiting]
Pensacola, Florida, United States, 32503

[Recruiting]
Sarasota, Florida, United States, 34239

[Not yet recruiting]
Stuart, Florida, United States, 34994

[Recruiting]
Sunrise, Florida, United States, 33351

[Not yet recruiting]
Tampa, Florida, United States, 33607

[Recruiting]
Tampa, Florida, United States, 33612

[Recruiting]
Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]
Augusta, Georgia, United States, 30909

[Not yet recruiting]

Marietta, Georgia, United States, 30060

United States, Hawaii

[Not yet recruiting]

Aiea, Hawaii, United States, 96701

[Not yet recruiting]

Honolulu, Hawaii, United States, 96813

United States, Illinois

[Not yet recruiting]

Chicago, Illinois, United States, 60611

[Not yet recruiting]

Chicago, Illinois, United States, 60637

[Recruiting]

Oak Brook, Illinois, United States, 60523

[Not yet recruiting]

Springfield, Illinois, United States, 62701

[Not yet recruiting]

Wheaton, Illinois, United States, 60187

United States, Indiana

[Not yet recruiting]

Ft. Wayne, Indiana, United States, 46804

[Not yet recruiting]

Indianapolis, Indiana, United States, 46202

[Not yet recruiting]

Indianapolis, Indiana, United States, 46260

[Recruiting]

Indianapolis, Indiana, United States, 46280

[Recruiting]

New Albany, Indiana, United States, 47150

United States, Iowa

[Not yet recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]
Wichita, Kansas, United States, 67214

United States, Kentucky

[Not yet recruiting]
Louisville, Kentucky, United States, 40202

[Not yet recruiting]
Louisville, Kentucky, United States, 40207

[Recruiting]
Paducah, Kentucky, United States, 42001

United States, Louisiana

[Not yet recruiting]
Metairie, Louisiana, United States, 70002

[Recruiting]
New Orleans, Louisiana, United States, 70115

[Not yet recruiting]
New Orleans, Louisiana, United States, 70121

[Not yet recruiting]
Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]
Bangor, Maine, United States, 04401

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Not yet recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Not yet recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Not yet recruiting]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Not yet recruiting]

Boston, Massachusetts, United States, 02215

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

[Not yet recruiting]

Battle Creek, Michigan, United States, 49015

[Not yet recruiting]

East Lansing, Michigan, United States, 48823

[Not yet recruiting]

Grand Blanc, Michigan, United States, 48439

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Not yet recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Not yet recruiting]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Recruiting]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Not yet recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Not yet recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Not yet recruiting]

Kansas City, Missouri, United States, 64111

[Not yet recruiting]

Springfield, Missouri, United States, 65804

[Not yet recruiting]

St. Louis, Missouri, United States, 63104

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]

Lincoln, Nebraska, United States, 68506

[Recruiting]

Omaha, Nebraska, United States, 68124

[Recruiting]

Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]

Las Vegas, Nevada, United States, 89144

United States, New Hampshire

[Not yet recruiting]

Lebanon, New Hampshire, United States, 03756

United States, New Jersey

[Recruiting]

Lawrenceville, New Jersey, United States, 08648

[Not yet recruiting]

Newark, New Jersey, United States, 07103

[Not yet recruiting]

Northfield, New Jersey, United States, 08225

[Recruiting]

Northfield, New Jersey, United States, 08225

[Recruiting]

Teaneck, New Jersey, United States, 07666

[Recruiting]

Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Not yet recruiting]

Albany, New York, United States, 12206

[Not yet recruiting]

Bronxville, New York, United States, 10708

[Not yet recruiting]

Bronx, New York, United States, 10467

[Not yet recruiting]

Brooklyn, New York, United States, 11223

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Not yet recruiting]

New York, New York, United States, 10032

[Recruiting]

Rochester, New York, United States, 14618

[Not yet recruiting]
Rochester, New York, United States, 14642

[Recruiting]
Slingerlands, New York, United States, 12159

United States, North Carolina

[Recruiting]
Asheville, North Carolina, United States, 28803

[Recruiting]
Charlotte, North Carolina, United States, 28210

[Not yet recruiting]
Hendersonville, North Carolina, United States, 28791

[Not yet recruiting]
Raleigh, North Carolina, United States, 27607

[Not yet recruiting]
Raleigh, North Carolina, United States, 27612

[Recruiting]
Southern Pines, North Carolina, United States, 28387

[Recruiting]
Winston-Salem, North Carolina, United States, 27157

United States, North Dakota

[Not yet recruiting]
Fargo, North Dakota, United States, 58103

United States, Ohio

[Not yet recruiting]
Canton, Ohio, United States, 44718

[Not yet recruiting]
Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Recruiting]

Cleveland, Ohio, United States, 44122

[Not yet recruiting]

Cleveland, Ohio, United States, 44195

[Not yet recruiting]

Columbus, Ohio, United States, 43215

[Not yet recruiting]

Toledo, Ohio, United States, 43606

[Recruiting]

Toledo, Ohio, United States, 43608

[Not yet recruiting]

Toledo, Ohio, United States, 43615

United States, Oklahoma

[Not yet recruiting]

Oklahoma City, Oklahoma, United States, 73104

[Not yet recruiting]

Tulsa, Oklahoma, United States, 74104

United States, Oregon

[Recruiting]

Ashland, Oregon, United States, 97520

[Not yet recruiting]

Portland, Oregon, United States, 97210

[Recruiting]

Portland, Oregon, United States, 97210

[Not yet recruiting]

Portland, Oregon, United States, 97227

[Not yet recruiting]

Salem, Oregon, United States, 97302

United States, Pennsylvania

[Not yet recruiting]
Camp Hill, Pennsylvania, United States, 17011

[Not yet recruiting]
Campbell, Pennsylvania, United States, 95008

[Not yet recruiting]
East Stroudsburg, Pennsylvania, United States, 18301

[Recruiting]
Kingston, Pennsylvania, United States, 18704

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19104

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19107

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19124

[Recruiting]
Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]
Pittsburgh, Pennsylvania, United States, 15213

[Not yet recruiting]
Pittsburgh, Pennsylvania, United States, 15219

[Recruiting]
Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]
Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Columbia, South Carolina, United States, 29204

[Recruiting]

Columbia, South Carolina, United States, 29223

[Not yet recruiting]

Greenville, South Carolina, United States, 29605

[Not yet recruiting]

Rock Hill, South Carolina, United States, 29732

United States, South Dakota

[Recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]

Memphis, Tennessee, United States, 38119

[Not yet recruiting]

Memphis, Tennessee, United States, 38120

[Recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]

Abilene, Texas, United States, 79606

[Recruiting]

Austin, Texas, United States, 78705

[Recruiting]

DeSoto, Texas, United States, 75115

[Recruiting]

Ft. Worth, Texas, United States, 76102

[Not yet recruiting]
Ft. Worth, Texas, United States, 76104

[Not yet recruiting]
Galveston, Texas, United States, 77555

[Recruiting]
Houston, Texas, United States, 77030

[Recruiting]
McAllen, Texas, United States, 78503

[Not yet recruiting]
Odessa, Texas, United States, 79761

[Recruiting]
San Antonio, Texas, United States, 78133

[Recruiting]
San Antonio, Texas, United States, 78240

United States, Utah

[Not yet recruiting]
Ogden, Utah, United States, 84403

[Recruiting]
Salt Lake City, Utah, United States, 84107

[Not yet recruiting]
Salt Lake City, Utah, United States, 84132

United States, Vermont

[Not yet recruiting]
Burlington, Vermont, United States, 05401

United States, Virginia

[Not yet recruiting]
Charlottesville, Virginia, United States, 22908

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]
Seattle, Washington, United States, 98104

[Not yet recruiting]
Seattle, Washington, United States, 98195

[Recruiting]
Silverdale, Washington, United States, 98383

[Not yet recruiting]
Spokane, Washington, United States, 99203

United States, Wisconsin

[Not yet recruiting]
Madison, Wisconsin, United States, 53715

[Not yet recruiting]
Madison, Wisconsin, United States, 58705

[Not yet recruiting]
Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Not yet recruiting]
Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Not yet recruiting]
Vancouver, British Columbia, Canada, V5Z 3N9

[Not yet recruiting]
Victoria, British Columbia, Canada, V8X 5G6

Canada, Nova Scotia

[Not yet recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Not yet recruiting]
London, Ontario, Canada, N6A 4G5

[Not yet recruiting]
Mississauga, Ontario, Canada, L4W 1W9

[Not yet recruiting]
Toronto, Ontario, Canada, M5C 2T2

[Recruiting]
Toronto, Ontario, Canada, M5T 2S8

Canada, Quebec

[Not yet recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Not yet recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Not yet recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine

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)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	◉	◉	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: December 4, 2007 (v4)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2007

Overall Status: Recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	December 4, 2007
Last Update Posted:	December 6, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap-Eye

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.

6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron

Telephone: 866-549-8439

Email: VIEW1study@rtp.ppdi.com

Study Officials: Avner Ingerman, MD

Study Director

Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Not yet recruiting]

Birmingham, Alabama, United States, 35205

[Not yet recruiting]

Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]

Phoenix, Arizona, United States, 85014

[Recruiting]

Phoenix, Arizona, United States, 85020

[Recruiting]

Tucson, Arizona, United States, 85704

[Not yet recruiting]

Tucson, Arizona, United States, 85710

[Not yet recruiting]

Tucson, Arizona, United States, 85711

United States, California

[Recruiting]

Beverly Hills, California, United States, 90211

[Not yet recruiting]

Fullerton, California, United States, 92835

[Not yet recruiting]

Glendale, California, United States, 91203

[Not yet recruiting]

Irvine, California, United States, 92697

[Not yet recruiting]

La Jolla, California, United States, 92037

[Recruiting]

Loma Linda, California, United States, 92354

[Not yet recruiting]

Los Angeles, California, United States, 90033

[Not yet recruiting]

Los Angeles, California, United States, 90048

[Not yet recruiting]

Menlo Park, California, United States, 94025

[Recruiting]

Mountain View, California, United States, 94040

[Recruiting]

Oakland, California, United States, 94609

[Recruiting]

Palm Springs, California, United States, 92262

[Recruiting]

Pasadena, California, United States, 91105

[Not yet recruiting]

Poway, California, United States, 92064

[Not yet recruiting]

Sacramento, California, United States, 95819

[Not yet recruiting]

San Diego, California, United States, 92120

[Recruiting]

San Francisco, California, United States, 94107

[Not yet recruiting]
San Marino, California, United States, 91108

[Recruiting]
Santa Ana, California, United States, 92705

[Not yet recruiting]
Ventura, California, United States, 93003

[Recruiting]
Westlake Village, California, United States, 91361

[Not yet recruiting]
Yorba Linda, California, United States, 92887

United States, Colorado

[Not yet recruiting]
Aurora, Colorado, United States, 80045

[Not yet recruiting]
Denver, Colorado, United States, 80205

[Not yet recruiting]
Denver, Colorado, United States, 80230

United States, Connecticut

[Not yet recruiting]
Bridgeport, Connecticut, United States, 06606

[Recruiting]
Hamden, Connecticut, United States, 06518

[Not yet recruiting]
New Haven, Connecticut, United States, 06520

[Recruiting]
New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Delray Beach, Florida, United States, 33484

[Recruiting]

Fort Myers, Florida, United States, 33907

[Not yet recruiting]

Ft. Lauderdale, Florida, United States, 33334

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Not yet recruiting]

Gainesville, Florida, United States, 32610

[Not yet recruiting]

Jacksonville, Florida, United States, 32216

[Not yet recruiting]

Jacksonville, Florida, United States, 32224

[Not yet recruiting]

Margate, Florida, United States, 33063

[Not yet recruiting]

Miami, Florida, United States, 33125

[Not yet recruiting]

Miami, Florida, United States, 33136

[Not yet recruiting]

Mount Dora, Florida, United States, 32757

[Not yet recruiting]

Ocala, Florida, United States, 34472

[Recruiting]
Orlando, Florida, United States, 32806

[Recruiting]
Orlando, Florida, United States, 38203

[Recruiting]
Palm Beach Gardens, Florida, United States, 33410

[Recruiting]
Pensacola, Florida, United States, 32503

[Recruiting]
Sarasota, Florida, United States, 34239

[Not yet recruiting]
Stuart, Florida, United States, 34994

[Recruiting]
Sunrise, Florida, United States, 33351

[Not yet recruiting]
Tampa, Florida, United States, 33607

[Recruiting]
Tampa, Florida, United States, 33612

[Recruiting]
Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]
Augusta, Georgia, United States, 30909

[Not yet recruiting]
Marietta, Georgia, United States, 30060

United States, Hawaii

[Not yet recruiting]
Aiea, Hawaii, United States, 96701

[Not yet recruiting]
Honolulu, Hawaii, United States, 96813

United States, Illinois

[Not yet recruiting]
Chicago, Illinois, United States, 60611

[Not yet recruiting]
Chicago, Illinois, United States, 60637

[Recruiting]
Oak Brook, Illinois, United States, 60523

[Not yet recruiting]
Springfield, Illinois, United States, 62701

[Not yet recruiting]
Wheaton, Illinois, United States, 60187

United States, Indiana

[Not yet recruiting]
Ft. Wayne, Indiana, United States, 46804

[Not yet recruiting]
Indianapolis, Indiana, United States, 46202

[Not yet recruiting]
Indianapolis, Indiana, United States, 46260

[Recruiting]
Indianapolis, Indiana, United States, 46280

[Recruiting]
New Albany, Indiana, United States, 47150

United States, Iowa

[Not yet recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]
Wichita, Kansas, United States, 67214

United States, Kentucky

[Not yet recruiting]
Louisville, Kentucky, United States, 40202

[Not yet recruiting]
Louisville, Kentucky, United States, 40207

[Recruiting]
Paducah, Kentucky, United States, 42001

United States, Louisiana

[Not yet recruiting]
Metairie, Louisiana, United States, 70002

[Recruiting]
New Orleans, Louisiana, United States, 70115

[Not yet recruiting]
New Orleans, Louisiana, United States, 70121

[Not yet recruiting]
Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]
Bangor, Maine, United States, 04401

United States, Maryland

[Recruiting]
Baltimore, Maryland, United States, 21209

[Not yet recruiting]
Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Not yet recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Not yet recruiting]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Not yet recruiting]

Boston, Massachusetts, United States, 02215

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

[Not yet recruiting]

Battle Creek, Michigan, United States, 49015

[Not yet recruiting]

East Lansing, Michigan, United States, 48823

[Not yet recruiting]

Grand Blanc, Michigan, United States, 48439

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Not yet recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Not yet recruiting]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Recruiting]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Not yet recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Not yet recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Not yet recruiting]

Kansas City, Missouri, United States, 64111

[Not yet recruiting]

Springfield, Missouri, United States, 65804

[Not yet recruiting]

St. Louis, Missouri, United States, 63104

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]
Lincoln, Nebraska, United States, 68506

[Recruiting]
Omaha, Nebraska, United States, 68124

[Recruiting]
Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]
Las Vegas, Nevada, United States, 89144

United States, New Hampshire

[Not yet recruiting]
Lebanon, New Hampshire, United States, 03756

United States, New Jersey

[Recruiting]
Lawrenceville, New Jersey, United States, 08648

[Not yet recruiting]
Newark, New Jersey, United States, 07103

[Not yet recruiting]
Northfield, New Jersey, United States, 08225

[Recruiting]
Northfield, New Jersey, United States, 08225

[Recruiting]
Teaneck, New Jersey, United States, 07666

[Recruiting]
Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Not yet recruiting]

Albany, New York, United States, 12206

[Not yet recruiting]

Bronxville, New York, United States, 10708

[Not yet recruiting]

Bronx, New York, United States, 10467

[Not yet recruiting]

Brooklyn, New York, United States, 11223

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Not yet recruiting]

New York, New York, United States, 10032

[Recruiting]

Rochester, New York, United States, 14618

[Not yet recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Not yet recruiting]

Hendersonville, North Carolina, United States, 28791

[Not yet recruiting]

Raleigh, North Carolina, United States, 27607

[Not yet recruiting]

Raleigh, North Carolina, United States, 27612

[Recruiting]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, North Dakota

[Not yet recruiting]

Fargo, North Dakota, United States, 58103

United States, Ohio

[Not yet recruiting]

Canton, Ohio, United States, 44718

[Not yet recruiting]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Recruiting]

Cleveland, Ohio, United States, 44122

[Not yet recruiting]

Cleveland, Ohio, United States, 44195

[Not yet recruiting]
Columbus, Ohio, United States, 43215

[Not yet recruiting]
Toledo, Ohio, United States, 43606

[Recruiting]
Toledo, Ohio, United States, 43608

[Not yet recruiting]
Toledo, Ohio, United States, 43615

United States, Oklahoma

[Not yet recruiting]
Oklahoma City, Oklahoma, United States, 73104

[Not yet recruiting]
Tulsa, Oklahoma, United States, 74104

United States, Oregon

[Recruiting]
Ashland, Oregon, United States, 97520

[Not yet recruiting]
Portland, Oregon, United States, 97210

[Recruiting]
Portland, Oregon, United States, 97210

[Not yet recruiting]
Portland, Oregon, United States, 97227

[Not yet recruiting]
Salem, Oregon, United States, 97302

United States, Pennsylvania

[Not yet recruiting]
Camp Hill, Pennsylvania, United States, 17011

[Not yet recruiting]

Campbell, Pennsylvania, United States, 95008

[Not yet recruiting]

East Stroudsburg, Pennsylvania, United States, 18301

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Not yet recruiting]

Pittsburgh, Pennsylvania, United States, 15219

[Recruiting]

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Columbia, South Carolina, United States, 29204

[Recruiting]

Columbia, South Carolina, United States, 29223

[Not yet recruiting]

Greenville, South Carolina, United States, 29605

[Not yet recruiting]
Rock Hill, South Carolina, United States, 29732

United States, South Dakota

[Recruiting]
Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]
Memphis, Tennessee, United States, 38119

[Not yet recruiting]
Memphis, Tennessee, United States, 38120

[Recruiting]
Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]
Abilene, Texas, United States, 79606

[Recruiting]
Austin, Texas, United States, 78705

[Recruiting]
DeSoto, Texas, United States, 75115

[Recruiting]
Ft. Worth, Texas, United States, 76102

[Not yet recruiting]
Ft. Worth, Texas, United States, 76104

[Not yet recruiting]
Galveston, Texas, United States, 77555

[Recruiting]
Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Not yet recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78133

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Not yet recruiting]

Ogden, Utah, United States, 84403

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Not yet recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Not yet recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Not yet recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Not yet recruiting]

Seattle, Washington, United States, 98195

[Recruiting]

Silverdale, Washington, United States, 98383

[Not yet recruiting]

Spokane, Washington, United States, 99203

United States, Wisconsin

[Not yet recruiting]

Madison, Wisconsin, United States, 53715

[Not yet recruiting]

Madison, Wisconsin, United States, 58705

[Not yet recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Not yet recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Not yet recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Not yet recruiting]

Victoria, British Columbia, Canada, V8X 5G6

Canada, Nova Scotia

[Not yet recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Not yet recruiting]

London, Ontario, Canada, N6A 4G5

[Not yet recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Not yet recruiting]
Toronto, Ontario, Canada, M5C 2T2

[Recruiting]
Toronto, Ontario, Canada, M5T 2S8

Canada, Quebec

[Not yet recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Not yet recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Not yet recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	◉	◉	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: November 14, 2007 (v3)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: August 2007

Overall Status: Recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	November 14, 2007
Last Update Posted:	November 16, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap-Eye

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.

6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Telephone: 866-549-8439
Email: VIEW1study@ppdi.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Not yet recruiting]
Birmingham, Alabama, United States, 35205

[Not yet recruiting]
Birmingham, Alabama, United States, 35223

United States, Arizona

[Recruiting]
Phoenix, Arizona, United States, 85014

[Recruiting]
Phoenix, Arizona, United States, 85020

[Recruiting]
Tucson, Arizona, United States, 85704

[Not yet recruiting]
Tucson, Arizona, United States, 85710

[Not yet recruiting]
Tucson, Arizona, United States, 85711

United States, California

[Recruiting]
Beverly Hills, California, United States, 90211

[Not yet recruiting]
Fullerton, California, United States, 92835

[Not yet recruiting]

Glendale, California, United States, 91203

[Not yet recruiting]
Irvine, California, United States, 92697

[Not yet recruiting]
La Jolla, California, United States, 92037

[Recruiting]
Loma Linda, California, United States, 92354

[Not yet recruiting]
Los Angeles, California, United States, 90033

[Not yet recruiting]
Los Angeles, California, United States, 90048

[Not yet recruiting]
Menlo Park, California, United States, 94025

[Recruiting]
Mountain View, California, United States, 94040

[Recruiting]
Oakland, California, United States, 94609

[Recruiting]
Palm Springs, California, United States, 92262

[Recruiting]
Pasadena, California, United States, 91105

[Not yet recruiting]
Poway, California, United States, 92064

[Not yet recruiting]
Sacramento, California, United States, 95819

[Not yet recruiting]
San Diego, California, United States, 92120

[Recruiting]

San Francisco, California, United States, 94107

[Not yet recruiting]
San Marino, California, United States, 91108

[Recruiting]
Santa Ana, California, United States, 92705

[Not yet recruiting]
Ventura, California, United States, 93003

[Recruiting]
Westlake Village, California, United States, 91361

[Not yet recruiting]
Yorba Linda, California, United States, 92887

United States, Colorado

[Not yet recruiting]
Aurora, Colorado, United States, 80045

[Not yet recruiting]
Denver, Colorado, United States, 80205

[Not yet recruiting]
Denver, Colorado, United States, 80230

United States, Connecticut

[Not yet recruiting]
Bridgeport, Connecticut, United States, 06606

[Recruiting]
Hamden, Connecticut, United States, 06518

[Not yet recruiting]
New Haven, Connecticut, United States, 06520

[Recruiting]
New London, Connecticut, United States, 06320

United States, Florida

[Recruiting]

Altamonte Springs, Florida, United States, 32701

[Recruiting]

Boynton Beach, Florida, United States, 33426

[Recruiting]

Delray Beach, Florida, United States, 33484

[Recruiting]

Fort Myers, Florida, United States, 33907

[Not yet recruiting]

Ft. Lauderdale, Florida, United States, 33334

[Recruiting]

Ft. Myers, Florida, United States, 33912

[Not yet recruiting]

Gainesville, Florida, United States, 32610

[Not yet recruiting]

Jacksonville, Florida, United States, 32216

[Not yet recruiting]

Jacksonville, Florida, United States, 32224

[Not yet recruiting]

Margate, Florida, United States, 33063

[Not yet recruiting]

Miami, Florida, United States, 33125

[Not yet recruiting]

Miami, Florida, United States, 33136

[Not yet recruiting]

Mount Dora, Florida, United States, 32757

[Not yet recruiting]

Ocala, Florida, United States, 34472

[Recruiting]
Orlando, Florida, United States, 32806

[Recruiting]
Orlando, Florida, United States, 38203

[Recruiting]
Palm Beach Gardens, Florida, United States, 33410

[Recruiting]
Pensacola, Florida, United States, 32503

[Recruiting]
Sarasota, Florida, United States, 34239

[Not yet recruiting]
Stuart, Florida, United States, 34994

[Recruiting]
Sunrise, Florida, United States, 33351

[Not yet recruiting]
Tampa, Florida, United States, 33607

[Recruiting]
Tampa, Florida, United States, 33612

[Recruiting]
Winter Haven, Florida, United States, 33880

United States, Georgia

[Recruiting]
Augusta, Georgia, United States, 30909

[Not yet recruiting]
Marietta, Georgia, United States, 30060

United States, Hawaii

[Not yet recruiting]
Aiea, Hawaii, United States, 96701

[Not yet recruiting]
Honolulu, Hawaii, United States, 96813

United States, Illinois

[Not yet recruiting]
Chicago, Illinois, United States, 60611

[Not yet recruiting]
Chicago, Illinois, United States, 60637

[Recruiting]
Oak Brook, Illinois, United States, 60523

[Not yet recruiting]
Springfield, Illinois, United States, 62701

[Not yet recruiting]
Wheaton, Illinois, United States, 60187

United States, Indiana

[Not yet recruiting]
Ft. Wayne, Indiana, United States, 46804

[Not yet recruiting]
Indianapolis, Indiana, United States, 46202

[Not yet recruiting]
Indianapolis, Indiana, United States, 46260

[Recruiting]
Indianapolis, Indiana, United States, 46280

[Recruiting]
New Albany, Indiana, United States, 47150

United States, Iowa

[Not yet recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Recruiting]

Wichita, Kansas, United States, 67214

United States, Kentucky

[Not yet recruiting]

Louisville, Kentucky, United States, 40202

[Not yet recruiting]

Louisville, Kentucky, United States, 40207

[Recruiting]

Paducah, Kentucky, United States, 42001

United States, Louisiana

[Not yet recruiting]

Metairie, Louisiana, United States, 70002

[Recruiting]

New Orleans, Louisiana, United States, 70115

[Not yet recruiting]

New Orleans, Louisiana, United States, 70121

[Not yet recruiting]

Shreveport, Louisiana, United States, 71105

United States, Maine

[Recruiting]

Bangor, Maine, United States, 04401

United States, Maryland

[Recruiting]

Baltimore, Maryland, United States, 21209

[Not yet recruiting]

Baltimore, Maryland, United States, 21287

[Recruiting]

Chevy Chase, Maryland, United States, 20815

[Not yet recruiting]

Hagerstown, Maryland, United States, 21740

[Recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Not yet recruiting]

Boston, Massachusetts, United States, 02111

[Recruiting]

Boston, Massachusetts, United States, 02114

[Not yet recruiting]

Boston, Massachusetts, United States, 02215

[Recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

[Not yet recruiting]

Battle Creek, Michigan, United States, 49015

[Not yet recruiting]

East Lansing, Michigan, United States, 48823

[Not yet recruiting]

Grand Blanc, Michigan, United States, 48439

[Recruiting]

Grand Rapids, Michigan, United States, 49525

[Not yet recruiting]

Jackson, Michigan, United States, 49201

[Recruiting]

Royal Oak, Michigan, United States, 48073

[Recruiting]

Southfield, Michigan, United States, 48034

[Not yet recruiting]

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Recruiting]

Edina, Minnesota, United States, 55435

[Recruiting]

Minneapolis, Minnesota, United States, 55404

[Not yet recruiting]

Rochester, Minnesota, United States, 55905

United States, Missouri

[Not yet recruiting]

Florissant, Missouri, United States, 63031

[Recruiting]

Kansas City, Missouri, United States, 64108

[Not yet recruiting]

Kansas City, Missouri, United States, 64111

[Not yet recruiting]

Springfield, Missouri, United States, 65804

[Not yet recruiting]

St. Louis, Missouri, United States, 63104

[Recruiting]

St. Louis, Missouri, United States, 63110

United States, Montana

[Recruiting]

Missoula, Montana, United States, 59801

United States, Nebraska

[Recruiting]
Lincoln, Nebraska, United States, 68506

[Recruiting]
Omaha, Nebraska, United States, 68124

[Recruiting]
Omaha, Nebraska, United States, 68131

United States, Nevada

[Recruiting]
Las Vegas, Nevada, United States, 89144

United States, New Hampshire

[Not yet recruiting]
Lebanon, New Hampshire, United States, 03756

United States, New Jersey

[Recruiting]
Lawrenceville, New Jersey, United States, 08648

[Not yet recruiting]
Newark, New Jersey, United States, 07103

[Not yet recruiting]
Northfield, New Jersey, United States, 08225

[Recruiting]
Northfield, New Jersey, United States, 08225

[Recruiting]
Teaneck, New Jersey, United States, 07666

[Recruiting]
Toms River, New Jersey, United States, 08753

United States, New Mexico

[Recruiting]

Albuquerque, New Mexico, United States, 87106

United States, New York

[Not yet recruiting]

Albany, New York, United States, 12206

[Not yet recruiting]

Bronxville, New York, United States, 10708

[Not yet recruiting]

Bronx, New York, United States, 10467

[Not yet recruiting]

Brooklyn, New York, United States, 11223

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Recruiting]

Lynbrook, New York, United States, 11563

[Recruiting]

New York, New York, United States, 10003

[Recruiting]

New York, New York, United States, 10021

[Not yet recruiting]

New York, New York, United States, 10032

[Recruiting]

Rochester, New York, United States, 14618

[Not yet recruiting]

Rochester, New York, United States, 14642

[Recruiting]

Slingerlands, New York, United States, 12159

United States, North Carolina

[Recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Not yet recruiting]

Hendersonville, North Carolina, United States, 28791

[Not yet recruiting]

Raleigh, North Carolina, United States, 27607

[Not yet recruiting]

Raleigh, North Carolina, United States, 27612

[Recruiting]

Southern Pines, North Carolina, United States, 28387

[Recruiting]

Winston-Salem, North Carolina, United States, 27157

United States, North Dakota

[Not yet recruiting]

Fargo, North Dakota, United States, 58103

United States, Ohio

[Not yet recruiting]

Canton, Ohio, United States, 44718

[Not yet recruiting]

Cincinnati, Ohio, United States, 45202

[Recruiting]

Cincinnati, Ohio, United States, 45242

[Recruiting]

Cleveland, Ohio, United States, 44122

[Not yet recruiting]

Cleveland, Ohio, United States, 44195

[Not yet recruiting]
Columbus, Ohio, United States, 43215

[Not yet recruiting]
Toledo, Ohio, United States, 43606

[Recruiting]
Toledo, Ohio, United States, 43608

[Not yet recruiting]
Toledo, Ohio, United States, 43615

United States, Oklahoma

[Not yet recruiting]
Oklahoma City, Oklahoma, United States, 73104

[Not yet recruiting]
Tulsa, Oklahoma, United States, 74104

United States, Oregon

[Recruiting]
Ashland, Oregon, United States, 97520

[Not yet recruiting]
Portland, Oregon, United States, 97210

[Recruiting]
Portland, Oregon, United States, 97210

[Not yet recruiting]
Portland, Oregon, United States, 97227

[Not yet recruiting]
Salem, Oregon, United States, 97302

United States, Pennsylvania

[Not yet recruiting]
Camp Hill, Pennsylvania, United States, 17011

[Not yet recruiting]

Campbell, Pennsylvania, United States, 95008

[Not yet recruiting]

East Stroudsburg, Pennsylvania, United States, 18301

[Recruiting]

Kingston, Pennsylvania, United States, 18704

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19104

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19107

[Not yet recruiting]

Philadelphia, Pennsylvania, United States, 19124

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15212

[Recruiting]

Pittsburgh, Pennsylvania, United States, 15213

[Not yet recruiting]

Pittsburgh, Pennsylvania, United States, 15219

[Recruiting]

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Recruiting]

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Recruiting]

Columbia, South Carolina, United States, 29204

[Recruiting]

Columbia, South Carolina, United States, 29223

[Not yet recruiting]

Greenville, South Carolina, United States, 29605

[Not yet recruiting]
Rock Hill, South Carolina, United States, 29732

United States, South Dakota

[Recruiting]
Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Recruiting]
Memphis, Tennessee, United States, 38119

[Not yet recruiting]
Memphis, Tennessee, United States, 38120

[Recruiting]
Nashville, Tennessee, United States, 37203

United States, Texas

[Recruiting]
Abilene, Texas, United States, 79606

[Recruiting]
Austin, Texas, United States, 78705

[Recruiting]
DeSoto, Texas, United States, 75115

[Recruiting]
Ft. Worth, Texas, United States, 76102

[Not yet recruiting]
Ft. Worth, Texas, United States, 76104

[Not yet recruiting]
Galveston, Texas, United States, 77555

[Recruiting]
Houston, Texas, United States, 77030

[Recruiting]

McAllen, Texas, United States, 78503

[Not yet recruiting]

Odessa, Texas, United States, 79761

[Recruiting]

San Antonio, Texas, United States, 78133

[Recruiting]

San Antonio, Texas, United States, 78240

United States, Utah

[Not yet recruiting]

Ogden, Utah, United States, 84403

[Recruiting]

Salt Lake City, Utah, United States, 84107

[Not yet recruiting]

Salt Lake City, Utah, United States, 84132

United States, Vermont

[Not yet recruiting]

Burlington, Vermont, United States, 05401

United States, Virginia

[Not yet recruiting]

Charlottesville, Virginia, United States, 22908

[Recruiting]

Richmond, Virginia, United States, 23221

United States, Washington

[Recruiting]

Seattle, Washington, United States, 98104

[Not yet recruiting]

Seattle, Washington, United States, 98195

[Recruiting]

Silverdale, Washington, United States, 98383

[Not yet recruiting]

Spokane, Washington, United States, 99203

United States, Wisconsin

[Not yet recruiting]

Madison, Wisconsin, United States, 53715

[Not yet recruiting]

Madison, Wisconsin, United States, 58705

[Not yet recruiting]

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Not yet recruiting]

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Not yet recruiting]

Vancouver, British Columbia, Canada, V5Z 3N9

[Not yet recruiting]

Victoria, British Columbia, Canada, V8X 5G6

Canada, Nova Scotia

[Not yet recruiting]

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Not yet recruiting]

London, Ontario, Canada, N6A 4G5

[Not yet recruiting]

Mississauga, Ontario, Canada, L4W 1W9

[Not yet recruiting]
Toronto, Ontario, Canada, M5C 2T2

[Recruiting]
Toronto, Ontario, Canada, M5T 2S8

Canada, Quebec

[Not yet recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Not yet recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Not yet recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	◉	◉	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: August 17, 2007 (v2)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: August 2007

Overall Status: Recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	August 17, 2007
Last Update Posted:	August 21, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap-Eye

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.

6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Central Contact: Regeneron
Email: vegf.trap@regeneron.com

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

[Not yet recruiting]
Birmingham, Alabama, United States, 35205

[Not yet recruiting]
Birmingham, Alabama, United States, 35223

United States, Arizona

[Not yet recruiting]
Phoenix, Arizona, United States, 85014

[Not yet recruiting]
Phoenix, Arizona, United States, 85020

[Not yet recruiting]
Tucson, Arizona, United States, 85704

[Not yet recruiting]
Tucson, Arizona, United States, 85710

[Not yet recruiting]
Tucson, Arizona, United States, 85711

United States, California

[Not yet recruiting]
Beverly Hills, California, United States, 90211

[Not yet recruiting]
Fullerton, California, United States, 92835

[Not yet recruiting]
Glendale, California, United States, 91203

[Not yet recruiting]
Irvine, California, United States, 92697

[Not yet recruiting]
La Jolla, California, United States, 92037

[Not yet recruiting]
Loma Linda, California, United States, 92354

[Not yet recruiting]
Los Angeles, California, United States, 90033

[Not yet recruiting]
Los Angeles, California, United States, 90048

[Not yet recruiting]
Menlo Park, California, United States, 94025

[Not yet recruiting]
Mountain View, California, United States, 94040

[Not yet recruiting]
Oakland, California, United States, 94609

[Not yet recruiting]
Palm Springs, California, United States, 92262

[Not yet recruiting]
Pasadena, California, United States, 91105

[Not yet recruiting]
Poway, California, United States, 92064

[Not yet recruiting]
Sacramento, California, United States, 95819

[Not yet recruiting]
San Diego, California, United States, 92120

[Not yet recruiting]
San Francisco, California, United States, 94107

[Not yet recruiting]
San Marino, California, United States, 91108

[Not yet recruiting]
Santa Ana, California, United States, 92705

[Not yet recruiting]
Ventura, California, United States, 93003

[Not yet recruiting]
Westlake Village, California, United States, 91361

[Not yet recruiting]
Yorba Linda, California, United States, 92887

United States, Colorado

[Not yet recruiting]
Aurora, Colorado, United States, 80045

[Not yet recruiting]
Denver, Colorado, United States, 80205

[Not yet recruiting]
Denver, Colorado, United States, 80230

United States, Connecticut

[Not yet recruiting]
Bridgeport, Connecticut, United States, 06606

[Not yet recruiting]
Hamden, Connecticut, United States, 06518

[Not yet recruiting]
New Haven, Connecticut, United States, 06520

[Not yet recruiting]
New London, Connecticut, United States, 06320

United States, Florida

[Not yet recruiting]

Altamonte Springs, Florida, United States, 32701

[Not yet recruiting]
Boynton Beach, Florida, United States, 33426

[Not yet recruiting]
Delray Beach, Florida, United States, 33484

[Not yet recruiting]
Fort Myers, Florida, United States, 33907

[Not yet recruiting]
Ft. Lauderdale, Florida, United States, 33334

[Not yet recruiting]
Ft. Myers, Florida, United States, 33912

[Not yet recruiting]
Gainesville, Florida, United States, 32610

[Not yet recruiting]
Jacksonville, Florida, United States, 32216

[Not yet recruiting]
Jacksonville, Florida, United States, 32224

[Not yet recruiting]
Margate, Florida, United States, 33063

[Not yet recruiting]
Miami, Florida, United States, 33125

[Not yet recruiting]
Miami, Florida, United States, 33136

[Not yet recruiting]
Mount Dora, Florida, United States, 32757

[Not yet recruiting]
Ocala, Florida, United States, 34472

[Not yet recruiting]

Orlando, Florida, United States, 32806

[Not yet recruiting]
Orlando, Florida, United States, 38203

[Not yet recruiting]
Palm Beach Gardens, Florida, United States, 33410

[Not yet recruiting]
Pensacola, Florida, United States, 32503

[Not yet recruiting]
Sarasota, Florida, United States, 34239

[Not yet recruiting]
Stuart, Florida, United States, 34994

[Not yet recruiting]
Sunrise, Florida, United States, 33351

[Not yet recruiting]
Tampa, Florida, United States, 33607

[Not yet recruiting]
Tampa, Florida, United States, 33612

[Not yet recruiting]
Winter Haven, Florida, United States, 33880

United States, Georgia

[Not yet recruiting]
Augusta, Georgia, United States, 30909

[Not yet recruiting]
Marietta, Georgia, United States, 30060

United States, Hawaii

[Not yet recruiting]
Aiea, Hawaii, United States, 96701

[Not yet recruiting]

Honolulu, Hawaii, United States, 96813

United States, Illinois

[Not yet recruiting]
Chicago, Illinois, United States, 60611

[Not yet recruiting]
Chicago, Illinois, United States, 60637

[Not yet recruiting]
Oak Brook, Illinois, United States, 60523

[Not yet recruiting]
Springfield, Illinois, United States, 62701

[Not yet recruiting]
Wheaton, Illinois, United States, 60187

United States, Indiana

[Not yet recruiting]
Ft. Wayne, Indiana, United States, 46804

[Not yet recruiting]
Indianapolis, Indiana, United States, 46202

[Not yet recruiting]
Indianapolis, Indiana, United States, 46260

[Not yet recruiting]
Indianapolis, Indiana, United States, 46280

[Not yet recruiting]
New Albany, Indiana, United States, 47150

United States, Iowa

[Not yet recruiting]
Iowa City, Iowa, United States, 52242-1091

United States, Kansas

[Not yet recruiting]
Wichita, Kansas, United States, 67214

United States, Kentucky

[Not yet recruiting]
Louisville, Kentucky, United States, 40202

[Not yet recruiting]
Louisville, Kentucky, United States, 40207

[Not yet recruiting]
Paducah, Kentucky, United States, 42001

United States, Louisiana

[Not yet recruiting]
Metairie, Louisiana, United States, 70002

[Not yet recruiting]
New Orleans, Louisiana, United States, 70115

[Not yet recruiting]
New Orleans, Louisiana, United States, 70121

[Not yet recruiting]
Shreveport, Louisiana, United States, 71105

United States, Maine

[Not yet recruiting]
Bangor, Maine, United States, 04401

United States, Maryland

[Not yet recruiting]
Baltimore, Maryland, United States, 21209

[Not yet recruiting]
Baltimore, Maryland, United States, 21287

[Not yet recruiting]
Chevy Chase, Maryland, United States, 20815

[Not yet recruiting]

Hagerstown, Maryland, United States, 21740

[Not yet recruiting]

Towson, Maryland, United States, 21204

United States, Massachusetts

[Not yet recruiting]

Boston, Massachusetts, United States, 02111

[Not yet recruiting]

Boston, Massachusetts, United States, 02114

[Not yet recruiting]

Boston, Massachusetts, United States, 02215

[Not yet recruiting]

Peabody, Massachusetts, United States, 01960

United States, Michigan

[Not yet recruiting]

Ann Arbor, Michigan, United States, 48105

[Not yet recruiting]

Battle Creek, Michigan, United States, 49015

[Not yet recruiting]

East Lansing, Michigan, United States, 48823

[Not yet recruiting]

Grand Blanc, Michigan, United States, 48439

[Not yet recruiting]

Grand Rapids, Michigan, United States, 49525

[Not yet recruiting]

Jackson, Michigan, United States, 49201

[Not yet recruiting]

Royal Oak, Michigan, United States, 48073

[Not yet recruiting]
Southfield, Michigan, United States, 48034

[Not yet recruiting]
West Bloomfield, Michigan, United States, 48322

United States, Minnesota

[Not yet recruiting]
Edina, Minnesota, United States, 55435

[Not yet recruiting]
Minneapolis, Minnesota, United States, 55404

[Not yet recruiting]
Rochester, Minnesota, United States, 55905

United States, Missouri

[Not yet recruiting]
Florissant, Missouri, United States, 63031

[Not yet recruiting]
Kansas City, Missouri, United States, 64108

[Not yet recruiting]
Kansas City, Missouri, United States, 64111

[Not yet recruiting]
Springfield, Missouri, United States, 65804

[Not yet recruiting]
St. Louis, Missouri, United States, 63104

[Not yet recruiting]
St. Louis, Missouri, United States, 63110

United States, Montana

[Not yet recruiting]
Missoula, Montana, United States, 59801

United States, Nebraska

[Not yet recruiting]
Lincoln, Nebraska, United States, 68506

[Not yet recruiting]
Omaha, Nebraska, United States, 68124

[Not yet recruiting]
Omaha, Nebraska, United States, 68131

United States, Nevada

[Not yet recruiting]
Las Vegas, Nevada, United States, 89144

United States, New Hampshire

[Not yet recruiting]
Lebanon, New Hampshire, United States, 03756

United States, New Jersey

[Not yet recruiting]
Lawrenceville, New Jersey, United States, 08648

[Not yet recruiting]
Newark, New Jersey, United States, 07103

[Not yet recruiting]
Northfield, New Jersey, United States, 08225

[Not yet recruiting]
Teaneck, New Jersey, United States, 07666

[Not yet recruiting]
Toms River, New Jersey, United States, 08753

United States, New Mexico

[Not yet recruiting]
Albuquerque, New Mexico, United States, 87106

United States, New York

[Not yet recruiting]

Albany, New York, United States, 12206

[Not yet recruiting]

Bronxville, New York, United States, 10708

[Not yet recruiting]

Bronx, New York, United States, 10467

[Not yet recruiting]

Brooklyn, New York, United States, 11223

[Not yet recruiting]

Great Neck, New York, United States, 11021

[Not yet recruiting]

Lynbrook, New York, United States, 11563

[Not yet recruiting]

New York, New York, United States, 10003

[Not yet recruiting]

New York, New York, United States, 10021

[Not yet recruiting]

New York, New York, United States, 10032

[Not yet recruiting]

Rochester, New York, United States, 14618

[Not yet recruiting]

Rochester, New York, United States, 14642

[Not yet recruiting]

Slingerlands, New York, United States, 12159

United States, North Carolina

[Not yet recruiting]

Asheville, North Carolina, United States, 28803

[Recruiting]

Charlotte, North Carolina, United States, 28210

[Not yet recruiting]
Hendersonville, North Carolina, United States, 28791

[Not yet recruiting]
Raleigh, North Carolina, United States, 27607

[Not yet recruiting]
Raleigh, North Carolina, United States, 27612

[Not yet recruiting]
Southern Pines, North Carolina, United States, 28387

[Not yet recruiting]
Winston-Salem, North Carolina, United States, 27157

United States, North Dakota

[Not yet recruiting]
Fargo, North Dakota, United States, 58103

United States, Ohio

[Not yet recruiting]
Canton, Ohio, United States, 44718

[Not yet recruiting]
Cincinnati, Ohio, United States, 45202

[Not yet recruiting]
Cincinnati, Ohio, United States, 45242

[Not yet recruiting]
Cleveland, Ohio, United States, 44122

[Not yet recruiting]
Cleveland, Ohio, United States, 44195

[Not yet recruiting]
Columbus, Ohio, United States, 43215

[Not yet recruiting]

Toledo, Ohio, United States, 43606

[Not yet recruiting]
Toledo, Ohio, United States, 43608

[Not yet recruiting]
Toledo, Ohio, United States, 43615

United States, Oklahoma

[Not yet recruiting]
Oklahoma City, Oklahoma, United States, 73104

[Not yet recruiting]
Tulsa, Oklahoma, United States, 74104

United States, Oregon

[Not yet recruiting]
Ashland, Oregon, United States, 97520

[Not yet recruiting]
Portland, Oregon, United States, 97210

[Not yet recruiting]
Portland, Oregon, United States, 97227

[Not yet recruiting]
Salem, Oregon, United States, 97302

United States, Pennsylvania

[Not yet recruiting]
Camp Hill, Pennsylvania, United States, 17011

[Not yet recruiting]
Campbell, Pennsylvania, United States, 95008

[Not yet recruiting]
East Stroudsburg, Pennsylvania, United States, 18301

[Not yet recruiting]
Kingston, Pennsylvania, United States, 18704

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19104

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19107

[Not yet recruiting]
Philadelphia, Pennsylvania, United States, 19124

[Not yet recruiting]
Pittsburgh, Pennsylvania, United States, 15212

[Not yet recruiting]
Pittsburgh, Pennsylvania, United States, 15213

[Not yet recruiting]
Pittsburgh, Pennsylvania, United States, 15219

[Not yet recruiting]
Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

[Not yet recruiting]
Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

[Not yet recruiting]
Columbia, South Carolina, United States, 29204

[Not yet recruiting]
Columbia, South Carolina, United States, 29223

[Not yet recruiting]
Greenville, South Carolina, United States, 29605

[Not yet recruiting]
Rock Hill, South Carolina, United States, 29732

United States, South Dakota

[Not yet recruiting]

Rapid City, South Dakota, United States, 57701

United States, Tennessee

[Not yet recruiting]

Memphis, Tennessee, United States, 38119

[Not yet recruiting]

Memphis, Tennessee, United States, 38120

[Not yet recruiting]

Nashville, Tennessee, United States, 37203

United States, Texas

[Not yet recruiting]

Abilene, Texas, United States, 79606

[Not yet recruiting]

Austin, Texas, United States, 78705

[Not yet recruiting]

DeSoto, Texas, United States, 75115

[Not yet recruiting]

Ft. Worth, Texas, United States, 76102

[Not yet recruiting]

Ft. Worth, Texas, United States, 76104

[Not yet recruiting]

Galveston, Texas, United States, 77555

[Recruiting]

Houston, Texas, United States, 77030

[Not yet recruiting]

McAllen, Texas, United States, 78503

[Not yet recruiting]

Odessa, Texas, United States, 79761

[Not yet recruiting]
San Antonio, Texas, United States, 78133

[Not yet recruiting]
San Antonio, Texas, United States, 78240

United States, Utah

[Not yet recruiting]
Ogden, Utah, United States, 84403

[Not yet recruiting]
Salt Lake City, Utah, United States, 84107

[Not yet recruiting]
Salt Lake City, Utah, United States, 84132

United States, Vermont

[Not yet recruiting]
Burlington, Vermont, United States, 05401

United States, Virginia

[Not yet recruiting]
Charlottesville, Virginia, United States, 22908

[Not yet recruiting]
Richmond, Virginia, United States, 23221

United States, Washington

[Not yet recruiting]
Seattle, Washington, United States, 98104

[Not yet recruiting]
Seattle, Washington, United States, 98195

[Not yet recruiting]
Silverdale, Washington, United States, 98383

[Not yet recruiting]
Spokane, Washington, United States, 99203

United States, Wisconsin

[Not yet recruiting]
Madison, Wisconsin, United States, 53715

[Not yet recruiting]
Madison, Wisconsin, United States, 58705

[Not yet recruiting]
Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

[Not yet recruiting]
Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

[Not yet recruiting]
Vancouver, British Columbia, Canada, V5Z 3N9

[Not yet recruiting]
Victoria, British Columbia, Canada, V8X 5G6

Canada, Nova Scotia

[Not yet recruiting]
Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

[Not yet recruiting]
London, Ontario, Canada, N6A 4G5

[Not yet recruiting]
Mississauga, Ontario, Canada, L4W 1W9

[Not yet recruiting]
Toronto, Ontario, Canada, M5C 2T2

[Not yet recruiting]
Toronto, Ontario, Canada, M5T 2S8

Canada, Quebec

[Not yet recruiting]
Montreal, Quebec, Canada, H1T 2M4

[Not yet recruiting]
Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

[Not yet recruiting]
Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	◉	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations
3	○	○	November 14, 2007	Contacts/Locations and Study Status

Version	A	B	Submitted Date	Changes
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: July 31, 2007 (v1)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: July 2007

Overall Status: Not yet recruiting

Study Start: August 2007

Primary Completion:

Study Completion:

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Last Update Submitted that Met QC Criteria:	July 31, 2007
Last Update Posted:	August 1, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.
Detailed Description:	

Conditions

Conditions:	Neovascular Age-Related Macular Degeneration
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	

Masking: Double (masked roles unspecified)

Allocation: Randomized

Enrollment: 1200 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap-Eye

Outcome Measures

Primary Outcome Measures:

1. Primary measure will be visual acuity changes compared to baseline

Secondary Outcome Measures:

2. Secondary measures will be angiographic and anatomical changes compared to baseline.

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.

6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents.
4. Total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1665 of 2000

Study Officials: Avner Ingerman, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

Tucson, Arizona, United States, 85711

United States, California

Beverly Hills, California, United States, 90211

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

San Marino, California, United States, 91108

Santa Ana, California, United States, 92705

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06520

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Delray Beach, Florida, United States, 33484

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33334

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32216

Jacksonville, Florida, United States, 32224

Margate, Florida, United States, 33063

Miami, Florida, United States, 33125

Miami, Florida, United States, 33136

Mount Dora, Florida, United States, 32757

Ocala, Florida, United States, 34472

Orlando, Florida, United States, 32806

Orlando, Florida, United States, 38203

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States, 34239

Stuart, Florida, United States, 34994

Sunrise, Florida, United States, 33351

Tampa, Florida, United States, 33607

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

Marietta, Georgia, United States, 30060

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Chicago, Illinois, United States, 60611

Chicago, Illinois, United States, 60637

Oak Brook, Illinois, United States, 60523

Springfield, Illinois, United States, 62701

Wheaton, Illinois, United States, 60187

United States, Indiana

Ft. Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

Metairie, Louisiana, United States, 70002

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

East Lansing, Michigan, United States, 48823

Grand Blanc, Michigan, United States, 48439

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63104

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68124

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Hampshire

Lebanon, New Hampshire, United States, 03756

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

Newark, New Jersey, United States, 07103

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Bronxville, New York, United States, 10708

Bronx, New York, United States, 10467

Brooklyn, New York, United States, 11223

Great Neck, New York, United States, 11021

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Rochester, New York, United States, 14618

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Hendersonville, North Carolina, United States, 28791

Raleigh, North Carolina, United States, 27607

Raleigh, North Carolina, United States, 27612

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, North Dakota

Fargo, North Dakota, United States, 58103

United States, Ohio

Canton, Ohio, United States, 44718

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Cleveland, Ohio, United States, 44122

Cleveland, Ohio, United States, 44195

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43606

Toledo, Ohio, United States, 43608

Toledo, Ohio, United States, 43615

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

Tulsa, Oklahoma, United States, 74104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Camp Hill, Pennsylvania, United States, 17011

Campbell, Pennsylvania, United States, 95008

East Stroudsburg, Pennsylvania, United States, 18301

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

Pittsburgh, Pennsylvania, United States, 15219

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Columbia, South Carolina, United States, 29204

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

Rock Hill, South Carolina, United States, 29732

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78133

San Antonio, Texas, United States, 78240

United States, Utah

Ogden, Utah, United States, 84403

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Seattle, Washington, United States, 98195

Silverdale, Washington, United States, 98383

Spokane, Washington, United States, 99203

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8X 5G6

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Toronto, Ontario, Canada, M5C 2T2

Toronto, Ontario, Canada, M5T 2S8

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	◉	◉	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: December 20, 2012 (v18)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2012

Overall Status: Completed

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Actual]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Results First Submitted:	December 16, 2011
Results First Submitted that Met QC Criteria:	April 13, 2012
Results First Posted:	April 16, 2012 [Estimate]
Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	December 20, 2012
Last Update Posted:	December 28, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase 3, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.

Detailed Description:

Conditions

Conditions: Macular Degeneration

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Interventional Study Model: Parallel Assignment

Number of Arms: 4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1217 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: ranibizumab 0.5mg Q4	Biological: ranibizumab Participants received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • Lucentis

Arms	Assigned Interventions
Experimental: aflibercept injection 2.0mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 0.5mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 0.5mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 2.0mg Q8	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) of: letter score of 73 to 25 (20/40 to 20/320) in the study eye at 4 meters.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key

Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.

5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links: URL: http://www.aaojournal.org/article/S0161-6420(12)00865-2/abstract
Description: Related Info

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	The study was conducted at 164 sites in the United States and Canada. Recruitment period: 02 Aug 2007 to 15 Sep 2009.

Pre-assignment Details	2063 patients were screened, 1217 randomized, and 1215 included in the Safety Analysis Set (SAF). The Full Analysis Set (FAS) included 1210 patients with at least 1 post-baseline assessment. The Per Protocol Set (PPS) included 1089 patients who received ≥ 9 doses of study drug and attended ≥ 9 scheduled visits during the first year.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and received sham injections at interim monthly visits.

Overall Study

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
Started	306	304	304	303
Patients Received Treatment (SAF)	304	304	304	303
Full Analysis Set (FAS) Population	304	304	301	301
Per Protocol Set (PPS) Population	269	285	270	265
Completed	284	293	277	276
Not Completed	22	11	27	27
Adverse Event	4	3	5	4
Death	3	1	2	7
Lack of Efficacy	0	0	2	2
Lost to Follow-up	1	2	4	4
OTHER	1	0	4	1
Protocol Violation	3	0	3	1
Withdrawal by Subject	10	5	7	8

Baseline Characteristics

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

Baseline Measures

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants		304	304	304	303	1215
Age Continuous [1] Mean (Standard Deviation) Unit of measure: years	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
		78.2 (0 to 0)	77.7 (0 to 0)	78.3 (0 to 0)	77.9 (0 to 0)	78.0 (8.00)
		[1] Measure Description: SAF population used for analysis.				
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	Female	172 56.58%	194 63.82%	169 55.59%	179 59.08%	714 58.77%
	Male	132 43.42%	110 36.18%	135 44.41%	124 40.92%	501 41.23%
Ethnicity (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	Hispanic or Latino	7 2.3% (0 to 0)	11 3.62% (0 to 0)	11 3.62% (0 to 0)	12 3.96% (0 to 0)	41 3.37%
	Not Hispanic or Latino	297 97.7%	293 96.38%	293 96.38%	291 96.04%	1174 96.63%
	Unknown or Not Reported	0 0%	0 0%	0 0%	0 0%	0 0%
		[1] Measure Description: SAF population used for analysis.				

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Race (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	American Indian or Alaska Native	2 0.66% (0 to 0)	0 0% (0 to 0)	2 0.66% (0 to 0)	1 0.33% (0 to 0)	5 0.41%
	Asian	0 0% (0 to 0)	3 0.99% (0 to 0)	5 1.64% (0 to 0)	4 1.32% (0 to 0)	12 0.99%
	Native Hawaiian or Other Pacific Islander	1 0.33% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	2 0.16%
	Black or African American	1 0.33% (0 to 0)	1 0.33% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	3 0.25%
	White	296 97.37% (0 to 0)	295 97.04% (0 to 0)	294 96.71% (0 to 0)	289 95.38% (0 to 0)	1174 96.63%
	More than one race	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	1 0.08%
	Unknown or Not Reported	4 1.32% (0 to 0)	5 1.64% (0 to 0)	3 0.99% (0 to 0)	6 1.98% (0 to 0)	18 1.48%
		[1] Measure Description: SAF population used for analysis.				
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1] Mean (Standard Deviation)	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Unit of measure: scores on a scale		71.7 (0 to 0)	70.4 (0 to 0)	71.1 (0 to 0)	69.5 (0 to 0)	70.7 (17.11)
		[1] Measure Description: SAF population used for analysis. The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.				
Baseline Area of Choroidal Neovascularization (CNV) [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.52 (0 to 0)	6.59 (0 to 0)	6.49 (0 to 0)	6.56 (0 to 0)	6.54 (4.968)
		[1] Measure Description: SAF population used for analysis.				
Baseline Lesion Type [1] Measure type: Number Unit of measure: patients	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Occult		115 (0 to 0)	110 (0 to 0)	123 (0 to 0)	118 (0 to 0)	466 38.35%
Minimally Classic		101 (0 to 0)	105 (0 to 0)	97 (0 to 0)	112 (0 to 0)	415 34.16%
Predominantly Classic		82 (0 to 0)	87 (0 to 0)	82 (0 to 0)	71 (0 to 0)	322 26.5%
Missing		6 (0 to 0)	2 (0 to 0)	2 (0 to 0)	2 (0 to 0)	12 0.99%
		[1] Measure Description: SAF population used for analysis.				
Baseline Total Lesion Size [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.99 (0 to 0)	6.98 (0 to 0)	6.96 (0 to 0)	6.88 (0 to 0)	6.95 (5.202)

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
		[1] Measure Description: SAF population used for analysis.				
Baseline Best Corrected Visual Acuity (BCVA) [1] Mean (Standard Deviation) Unit of measure: letters read	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
		54.0 (0 to 0)	55.2 (0 to 0)	55.5 (0 to 0)	55.7 (0 to 0)	55.1 (13.14)
		[1] Measure Description: SAF population used for analysis. BCVA assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For BCVA tested via the 4 meter ETDRS protocol, 83 letters or more would represent 20/20 vision or better which would be considered an excellent outcome. Although, the ETDRS charts include 100 letters as the maximum possible score. The worst outcome is 0 letters read.				

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)
Measure Description	Defined "maintenance of vision" as patients who lost fewer than 15 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline.
Time Frame	Baseline and at week 52

Analysis Population Description

PPS population used for analysis.

Reporting Groups

	Description

Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	269	285	270	265	1089
Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF) Measure Type: Number Unit of Measure: percentage of patients	94.4 (0)	95.1 (0)	95.9 (0)	95.1 (0)	95.1 (0)

Statistical Analysis 1 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI.
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.4 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A positive value favors IAI 2.0Q4. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 2 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI (EYLEA, VEGF Trap-Eye).
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95.1% -5.1 to 2.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A negative value favors the IAI 0.5Q4 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 3 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI (EYLEA, VEGF Trap-Eye).
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.5 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A negative value favors the IAI 2.0Q8 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

2. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	8.1 (15.25)	10.9 (13.77)	6.9 (13.41)	7.9 (15.00)	8.5 (14.44)

Statistical Analysis 1 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0054
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	3.15
	Confidence Interval	(2-sided) 95.1% 0.92 to 5.37
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4793
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.80
	Confidence Interval	(2-sided) 95.1% -3.03 to 1.43
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8179
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares Means
	Estimated Value	0.26
	Confidence Interval	(2-sided) 95.1% -1.97 to 2.49
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q8.

3. Secondary Outcome Measure:

Measure Title	Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF. Measure Type: Number Unit of Measure: percentage of patients	30.9 (0)	37.5 (0)	24.9 (0)	30.6 (0)	31.1 (0)

Statistical Analysis 1 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1042
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	6.6
	Confidence Interval	(2-sided) 95.1% -1.0 to 14.1
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1037
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-6.0
	Confidence Interval	(2-sided) 95.1% -13.2 to 1.2
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.93
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.4
	Confidence Interval	(2-sided) 95.1% -7.7 to 7.0
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q8.

4. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.
Time Frame	Baseline and at Week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: scores on a scale	4.9 (14.01)	6.7 (13.50)	4.5 (11.87)	5.1 (14.74)	5.3 (13.59)

Statistical Analysis 1 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2090
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences Least Squares means
	Estimated Value	1.28
	Confidence Interval	(2-sided) 95.1% -0.73 to 3.28
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5128
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.67
	Confidence Interval	(2-sided) 95.1% -2.69 to 1.35
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5579
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.60
	Confidence Interval	(2-sided) 95.1% -2.61 to 1.42
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q8.

5. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)
Measure Description	CNV area values measured in square millimeters (mm^2); lower values represent better outcomes.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: mm^2	-4.2 (5.59)	-4.6 (5.47)	-3.5 (5.27)	-3.4 (6.02)	-3.9 (5.61)

Statistical Analysis 1 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3575
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.33
	Confidence Interval	(2-sided) 95.1% -1.04 to 0.38
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 2.0Q4

Statistical Analysis 2 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0507
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.71
	Confidence Interval	(2-sided) 95.1% -0.01 to 1.42
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 0.5Q4

Statistical Analysis 3 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0173
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.86
	Confidence Interval	(2-sided) 95.1% 0.15 to 1.58
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 2.0Q8

Reported Adverse Events

Time Frame	AEs reported from Day 1 to Wk 96. Yr 1 of tx (Day 1 to Wk 52): 21-day screening period followed by administration of study drug every 4 or 8 wks including sham injections at interim study visits (when study drug was not administered) for 48 wks.
Adverse Event Reporting Description	Yr 2 of tx (Wk 52 to Wk 96): Pts evaluated every 4 wks and received IVT injections of study drug (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 wks.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of ranibizumab (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.

IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.

All-Cause Mortality

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/

Serious Adverse Events

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	94/304 (30.92%)	70/304 (23.03%)	88/304 (28.95%)	90/303 (29.7%)
Blood and lymphatic system disorders				
ANAEMIA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
COAGULOPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Congenital, familial and genetic disorders				

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ARTERIOVENOUS MALFORMATION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Ear and labyrinth disorders				
ACUTE CORONARY SYNDROME [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
ACUTE MYOCARDIAL INFARCTION [A*]	1/304 (0.33%)	2/304 (0.66%)	2/304 (0.66%)	1/303 (0.33%)
ANGINA UNSTABLE [A*]	3/304 (0.99%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
AORTIC VALVE STENOSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ARRHYTHMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ARTERIOSCLEROSIS CORONARY ARTERY [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ATRIAL FIBRILLATION [A*]	3/304 (0.99%)	2/304 (0.66%)	7/304 (2.3%)	7/303 (2.31%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BRADYCARDIA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CARDIAC ARREST [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
CARDIAC FAILURE ACUTE [A*]	1/304 (0.33%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
CARDIAC FAILURE CHRONIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CARDIAC FAILURE CONGESTIVE [A*]	4/304 (1.32%)	2/304 (0.66%)	4/304 (1.32%)	8/303 (2.64%)
CARDIO-RESPIRATORY ARREST [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CARDIOMYOPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CORONARY ARTERY DISEASE [A*]	5/304 (1.64%)	0/304 (0%)	6/304 (1.97%)	1/303 (0.33%)
CORONARY ARTERY OCCLUSION [A*]	1/304 (0.33%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
CORONARY ARTERY STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
INTRACARDIAC THROMBUS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MENIERE'S DISEASE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MITRAL VALVE INCOMPETENCE [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
MYOCARDIAL INFARCTION [A*]	6/304 (1.97%)	1/304 (0.33%)	5/304 (1.64%)	2/303 (0.66%)
MYOCARDIAL ISCHAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PERICARDIAL EFFUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SICK SINUS SYNDROME [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUPRAVENTRICULAR TACHYCARDIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TACHYARRHYTHMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
TACHYCARDIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
VENTRICULAR FIBRILLATION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VENTRICULAR TACHYCARDIA [A*]	0/304 (0%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
VERTIGO [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
Eye disorders				
AGE-RELATED MACULAR DEGENERATION [A [1]*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ANGLE CLOSURE GLAUCOMA [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BLEPHARITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BLINDNESS TRANSIENT [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CATARACT [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOROIDAL HAEMORRHAGE [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOROIDAL NEOVASCULARISATION [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONJUNCTIVAL HAEMORRHAGE [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONJUNCTIVITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DRY Eye disorders [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders IRRITATION [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders PAIN [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders PRURITUS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOREIGN BODY SENSATION IN Eye disordersS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
KERATITIS [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LACRIMATION INCREASED [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MACULAR DEGENERATION [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MACULAR HOLE [A] [2]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MACULOPATHY [A] [1]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
POSTERIOR CAPSULE OPACIFICATION [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PSEUDOENDOPHTHALMITIS [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL DEGENERATION [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RETINAL DETACHMENT [A] [1]*	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
RETINAL HAEMORRHAGE [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL OEDEMA [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL PIGMENT EPITHELIAL TEar and labyrinth disorders [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL PIGMENT EPITHELIOPATHY [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL TEar and labyrinth disorders [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
UVEITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
VISION BLURRED [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VISUAL ACUITY REDUCED [A] [1]*	1/304 (0.33%)	1/304 (0.33%)	3/304 (0.99%)	0/303 (0%)
VITREOUS DETACHMENT [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VITREOUS FLOATERS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VITREOUS HAEMORRHAGE [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Gastrointestinal disorders				
ABDOMINAL HERNIA [A]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ABDOMINAL HERNIA OBSTRUCTIVE [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ASTHENIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CATHETER SITE HAEMATOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CHEST PAIN [A*]	2/304 (0.66%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
COLITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
COLITIS ISCHAEMIC [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
COLONIC POLYP [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONSTIPATION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DEATH [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
DEVICE DISLOCATION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
DIARRHOEA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DRUG WITHDRAWAL SYNDROME [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DUODENAL ULCER HAEMORRHAGE [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DYSPHAGIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOOD POISONING [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
GASTRIC HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTRIC ULCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS EROSIVE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
GASTROINTESTINAL DISORDER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
GASTROINTESTINAL MOTILITY DISORDER [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROINTESTINAL OBSTRUCTION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
GASTROOESOPHAGEAL REFLUX DISEASE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMATOCHEZIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMORRHOIDS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HIATUS HERNIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ILEUS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
INGUINAL HERNIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INTESTINAL OBSTRUCTION [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
LOWER GASTROINTESTINAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
NAUSEA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
NON-CARDIAC CHEST PAIN [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
OESOPHAGEAL ULCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PANCREATITIS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
PYREXIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SMALL INTESTINAL OBSTRUCTION [A*]	2/304 (0.66%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
Hepatobiliary disorders				
BILE DUCT STONE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CHOLANGITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHOLECYSTITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
CHOLECYSTITIS ACUTE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOLECYSTITIS CHRONIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHOLELITHIASIS [A*]	1/304 (0.33%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
PORTAL HYPERTENSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PORTAL VEIN THROMBOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Immune system disorders				
DRUG HYPERSENSITIVITY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Infections and infestations				
ANAL ABSCESS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ANORECTAL CELLULITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ARTHRITIS BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
BACTERIAL DISEASE CARRIER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BRONCHITIS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	3/303 (0.99%)
CELLULITIS [A*]	3/304 (0.99%)	3/304 (0.99%)	2/304 (0.66%)	0/303 (0%)
CLOSTRIDIAL Infections and infestationsION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
CLOSTRIDIUM DIFFICILE COLITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DEVICE RELATED Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
DIVERTICULITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
ENCEPHALITIS VIRAL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOCARDITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOPHTHALMITIS [A [1]*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ESCHERICHIA URINARY TRACT Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROENTERITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
GASTROENTERITIS VIRAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
INFLUENZA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
KLEBSIELLA BACTERAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LABYRINTHITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LOBAR PNEUMONIA [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
LUNG Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
NASOPHARYNGITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PHARYNGITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PNEUMONIA [A*]	14/304 (4.61%)	6/304 (1.97%)	5/304 (1.64%)	8/303 (2.64%)
PYELONEPHRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SCROTAL ABSCESS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SEPSIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SEPTIC SHOCK [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SINUSITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SINUSITIS FUNGAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
STAPHYLOCOCCAL BACTERAEMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
UPPER RESPIRATORY TRACT Infections and infestationsION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
URINARY TRACT Infections and infestationsION [A*]	1/304 (0.33%)	3/304 (0.99%)	0/304 (0%)	0/303 (0%)
URINARY TRACT Infections and infestationsION BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
URINARY TRACT Infections and infestationsION STAPHYLOCOCCAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
UROSEPSIS [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
VESTIBULAR NEURONITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL Infections and infestationsION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL PERICARDITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
WOUND Infections and infestationsION BACTERIAL [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Injury, poisoning and procedural complications				
ACCIDENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CERVICAL VERTEBRAL FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONCUSSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
FALL [A*]	8/304 (2.63%)	13/304 (4.28%)	7/304 (2.3%)	16/303 (5.28%)
FEMORAL NECK FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
FEMUR FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
FIBULA FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOOT FRACTURE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
HEAD Injury, poisoning and procedural complications [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HIP FRACTURE [A*]	1/304 (0.33%)	4/304 (1.32%)	2/304 (0.66%)	1/303 (0.33%)
HUMERUS FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	3/304 (0.99%)	0/303 (0%)
INCISIONAL HERNIA, OBSTRUCTIVE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INCORRECT DOSE ADMINISTERED [A [2]*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
JOINT DISLOCATION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
JOINT Injury, poisoning and procedural complications [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LUMBAR VERTEBRAL FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MENISCUS LESION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
POST LAMINECTOMY SYNDROME [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PROCEDURAL PAIN [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PUBIS FRACTURE [A*]	1/304 (0.33%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
RIB FRACTURE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
ROAD TRAFFIC ACCIDENT [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SNAKE BITE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SPINAL COMPRESSION FRACTURE [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
SPINAL FRACTURE [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
STERNAL FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SUBCUTANEOUS HAEMATOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUBDURAL HAEMATOMA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
TIBIA FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
TRAUMATIC BRAIN Injury, poisoning and procedural complications [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
UPPER LIMB FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
VASCULAR PSEUDOANEURYSM [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Investigations				
Blood and lymphatic system disorders GLUCOSE INCREASED [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Blood and lymphatic system disorders PRESSURE INCREASED [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
Blood and lymphatic system disorders PRESSURE ORTHOSTATIC ABNORMAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
INTRAOCULAR PRESSURE INCREASED [A [1]*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Metabolism and nutrition disorders				
DEHYDRATION [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
DIABETES MELLITUS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
DIABETES MELLITUS INADEQUATE CONTROL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ELECTROLYTE IMBALANCE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPERKALAEMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HYPOGLYCAEMIA [A*]	0/304 (0%)	2/304 (0.66%)	1/304 (0.33%)	0/303 (0%)
HYPOKALAEMIA [A*]	2/304 (0.66%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPONATRAEMIA [A*]	2/304 (0.66%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
MALNUTRITION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HYPOGLYCAEMIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Musculoskeletal and connective tissue disorders				
ARTHRALGIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ARTHRITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
ARTHROPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BACK PAIN [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CERVICAL SPINAL STENOSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
INTERVERTEBRAL DISC DEGENERATION [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
INTERVERTEBRAL DISC PROTRUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUMBAR SPINAL STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
OSTEOARTHRITIS [A*]	4/304 (1.32%)	1/304 (0.33%)	3/304 (0.99%)	1/303 (0.33%)
OSTEONECROSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PAIN IN EXTREMITY [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RHABDOMYOLYSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SPINAL COLUMN STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPINAL OSTEOARTHRITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPONDYLOLISTHESIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
ATYPICAL FIBROXANTHOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
B-CELL LYMPHOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BASAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BLADDER TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	2/304 (0.66%)	1/303 (0.33%)
BLADDER TRANSITIONAL CELL CARCINOMA RECURRENT [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BRAIN NEOPLASM [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
BREAST Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	2/303 (0.66%)
BREAST Neoplasms benign, malignant and unspecified (incl cysts and polyps) IN SITU [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
BRONCHIOLOALVEOLAR CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CARDIAC MYXOMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CHRONIC LYMPHOCYTIC LEUKAEMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
COLON Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
COLON Neoplasms benign, malignant and unspecified (incl cysts and polyps) RECURRENT [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOMETRIAL Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
HEPATIC NEOPLASM MALIGNANT [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HEPATIC Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LEUKAEMIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
LUNG NEOPLASM [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUNG NEOPLASM MALIGNANT [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
LUNG SQUAMOUS CELL CARCINOMA STAGE II [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MALIGNANT MELANOMA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTASES TO CENTRAL NERVOUS SYSTEM [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
METASTASES TO Hepatobiliary disorders [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTASES TO LUNG [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
METASTASES TO LYMPH NODES [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTATIC NEOPLASM [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
NEOPLASM MALIGNANT [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
NON-SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
NON-SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) STAGE IV [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
OESOPHAGEAL ADENOCARCINOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
PROSTATE Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	1/304 (0.33%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
PROSTATE Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
RECTAL Neoplasms benign, malignant and unspecified (incl cysts and polyps) STAGE III [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
RECTOSIGMOID Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RENAL CELL CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SALIVARY GLAND Neoplasms benign, malignant and unspecified (incl cysts and polyps) RECURRENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SMALL CELL LUNG Neoplasms benign,malignant & unspecified(incl cysts and polyps)STAGE UNSPECIFIED [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SQUAMOUS CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SQUAMOUS CELL CARCINOMA OF Skin and subcutaneous tissue disorders [A*]	5/304 (1.64%)	3/304 (0.99%)	2/304 (0.66%)	4/303 (1.32%)
THYROID Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TONSIL Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TUMOUR HAEMORRHAGE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
WALDENSTROM'S MACROGLOBULINAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Nervous system disorders				
APHASIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BALANCE DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CAROTID ARTERY DISEASE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CAROTID ARTERY STENOSIS [A*]	0/304 (0%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
CEREBELLAR INFARCTION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CEREBRAL ARTERY THROMBOSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CEREBRAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBRAL INFARCTION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBROVASCULAR ACCIDENT [A*]	2/304 (0.66%)	3/304 (0.99%)	1/304 (0.33%)	5/303 (1.65%)
COMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONVULSION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DEMENTIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DIZZINESS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
EMBOLIC STROKE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HEADACHE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ISCHAEMIC CEREBRAL INFARCTION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LACUNAR INFARCTION [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LOSS OF CONSCIOUSNESS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
METABOLIC ENCEPHALOPATHY [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PRESYNCOPE [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
SPINAL CORD COMPRESSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SUBARACHNOID HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
SYNCOPE [A*]	3/304 (0.99%)	1/304 (0.33%)	3/304 (0.99%)	1/303 (0.33%)
TRANSIENT GLOBAL AMNESIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
TRANSIENT ISCHAEMIC ATTACK [A*]	0/304 (0%)	3/304 (0.99%)	7/304 (2.3%)	5/303 (1.65%)
Psychiatric disorders				
CONFUSIONAL STATE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MENTAL STATUS CHANGES [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Psychiatric disordersOTIC DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Renal and urinary disorders				
CALCULUS BLADDER [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CALCULUS URETERIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HAEMATURIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HYDRONEPHROSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RENAL FAILURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RENAL FAILURE ACUTE [A*]	0/304 (0%)	3/304 (0.99%)	2/304 (0.66%)	2/303 (0.66%)
RENAL FAILURE CHRONIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Reproductive system and breast disorders				
CYSTOCELE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RECTOCELE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Respiratory, thoracic and mediastinal disorders				
ACUTE RESPIRATORY FAILURE [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
APNOEIC ATTACK [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ASTHMA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CHRONIC OBSTRUCTIVE PULMONARY DISEASE [A*]	3/304 (0.99%)	3/304 (0.99%)	6/304 (1.97%)	6/303 (1.98%)
COUGH [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
DYSPNOEA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
EMPHYSEMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PLEURAL EFFUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PNEUMONIA ASPIRATION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
PNEUMONITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
PULMONARY EMBOLISM [A*]	0/304 (0%)	2/304 (0.66%)	1/304 (0.33%)	2/303 (0.66%)
PULMONARY FIBROSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PULMONARY MASS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PULMONARY OEDEMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RESPIRATORY DISTRESS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RESPIRATORY FAILURE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RESTRICTIVE PULMONARY DISEASE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TRACHEAL MASS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Skin and subcutaneous tissue disorders				
ANGIOEDEMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
Surgical and medical procedures				
CHOLECYSTECTOMY [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
MICROGRAPHIC Skin and subcutaneous tissue disorders SURGERY [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
Vascular disorders				
AORTIC ANEURYSM [A*]	1/304 (0.33%)	2/304 (0.66%)	1/304 (0.33%)	0/303 (0%)
AORTIC ANEURYSM RUPTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
AORTIC STENOSIS [A*]	1/304 (0.33%)	1/304 (0.33%)	2/304 (0.66%)	1/303 (0.33%)
ARTERIOSCLEROSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DEEP VEIN THROMBOSIS [A*]	1/304 (0.33%)	1/304 (0.33%)	1/304 (0.33%)	2/303 (0.66%)
FEMORAL ARTERY ANEURYSM [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HAEMATOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPERTENSION [A*]	2/304 (0.66%)	0/304 (0%)	3/304 (0.99%)	0/303 (0%)
HYPOTENSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ILIAC ARTERY OCCLUSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
LYMPHATIC FISTULA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LYMPHOCELE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ORTHOSTATIC HYPOTENSION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PERIPHERAL ARTERY ANEURYSM [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PERIPHERAL VASCULAR DISORDER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PHLEBITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
PHLEBITIS DEEP A*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HAEMORRHAGIC A*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, Medra Version 14.0

[1] Ocular Fellow Eye disorders

[2] Ocular Study Eye disorders

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	261/304 (85.86%)	254/304 (83.55%)	262/304 (86.18%)	258/303 (85.15%)
Ear and labyrinth disorders				
ATRIOVENTRICULAR BLOCK FIRST DEGREE A*	16/304 (5.26%)	18/304 (5.92%)	8/304 (2.63%)	9/303 (2.97%)
Eye disorders				
AGE-RELATED MACULAR DEGENERATION A [1]*	21/304 (6.91%)	16/304 (5.26%)	12/304 (3.95%)	15/303 (4.95%)
BLEPHARITIS A [1]*	16/304 (5.26%)	18/304 (5.92%)	14/304 (4.61%)	14/303 (4.62%)
CATARACT A [1]*	10/304 (3.29%)	17/304 (5.59%)	10/304 (3.29%)	10/303 (3.3%)
CHOROIDAL NEOVASCULARISATION A [1]*	17/304 (5.59%)	10/304 (3.29%)	13/304 (4.28%)	9/303 (2.97%)
CONJUNCTIVAL HAEMORRHAGE A [1]*	16/304 (5.26%)	17/304 (5.59%)	16/304 (5.26%)	19/303 (6.27%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
DRY Eye disorders [A] [2]*	12/304 (3.95%)	16/304 (5.26%)	10/304 (3.29%)	14/303 (4.62%)
Eye disorders IRRITATION [A] [2]*	19/304 (6.25%)	13/304 (4.28%)	15/304 (4.93%)	16/303 (5.28%)
Eye disorders PAIN [A] [2]*	34/304 (11.18%)	39/304 (12.83%)	35/304 (11.51%)	31/303 (10.23%)
Eye disorders PRURITUS [A] [2]*	11/304 (3.62%)	16/304 (5.26%)	10/304 (3.29%)	6/303 (1.98%)
FOREIGN BODY SENSATION IN Eye disordersS [A] [2]*	9/304 (2.96%)	10/304 (3.29%)	10/304 (3.29%)	19/303 (6.27%)
LACRIMATION INCREASED [A] [2]*	11/304 (3.62%)	11/304 (3.62%)	15/304 (4.93%)	16/303 (5.28%)
MACULAR DEGENERATION [A] [1]*	22/304 (7.24%)	14/304 (4.61%)	21/304 (6.91%)	14/303 (4.62%)
RETINAL HAEMORRHAGE [A] [1]*	43/304 (14.14%)	36/304 (11.84%)	36/304 (11.84%)	22/303 (7.26%)
RETINAL OEDEMA [A] [1]*	18/304 (5.92%)	8/304 (2.63%)	12/304 (3.95%)	11/303 (3.63%)
RETINAL PIGMENT EPITHELIOPATHY [A] [2]*	14/304 (4.61%)	18/304 (5.92%)	17/304 (5.59%)	14/303 (4.62%)
VISION BLURRED [A] [2]*	12/304 (3.95%)	18/304 (5.92%)	17/304 (5.59%)	13/303 (4.29%)
VISUAL ACUITY REDUCED [A] [1]*	27/304 (8.88%)	10/304 (3.29%)	20/304 (6.58%)	19/303 (6.27%)
VITREOUS DETACHMENT [A] [1]*	16/304 (5.26%)	24/304 (7.89%)	25/304 (8.22%)	24/303 (7.92%)
VITREOUS FLOATERS [A] [2]*	47/304 (15.46%)	49/304 (16.12%)	30/304 (9.87%)	29/303 (9.57%)
Gastrointestinal disorders				
DIARRHOEA [A]*	18/304 (5.92%)	18/304 (5.92%)	8/304 (2.63%)	9/303 (2.97%)
NAUSEA [A]*	15/304 (4.93%)	16/304 (5.26%)	15/304 (4.93%)	15/303 (4.95%)
Infections and infestations				
BRONCHITIS [A]*	23/304 (7.57%)	19/304 (6.25%)	16/304 (5.26%)	24/303 (7.92%)
NASOPHARYNGITIS [A]*	36/304 (11.84%)	46/304 (15.13%)	41/304 (13.49%)	39/303 (12.87%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SINUSITIS [A*]	18/304 (5.92%)	13/304 (4.28%)	17/304 (5.59%)	14/303 (4.62%)
UPPER RESPIRATORY TRACT Infections and infestationsION [A*]	18/304 (5.92%)	18/304 (5.92%)	19/304 (6.25%)	26/303 (8.58%)
URINARY TRACT Infections and infestationsION [A*]	26/304 (8.55%)	22/304 (7.24%)	25/304 (8.22%)	23/303 (7.59%)
Injury, poisoning and procedural complications				
FALL [A*]	19/304 (6.25%)	13/304 (4.28%)	15/304 (4.93%)	21/303 (6.93%)
Investigations				
Blood and lymphatic system disorders GLUCOSE INCREASED [A*]	13/304 (4.28%)	12/304 (3.95%)	17/304 (5.59%)	16/303 (5.28%)
INTRAOCULAR PRESSURE INCREASED [A [1]*]	16/304 (5.26%)	8/304 (2.63%)	15/304 (4.93%)	15/303 (4.95%)
Musculoskeletal and connective tissue disorders				
ARTHRALGIA [A*]	17/304 (5.59%)	18/304 (5.92%)	17/304 (5.59%)	8/303 (2.64%)
BACK PAIN [A*]	11/304 (3.62%)	14/304 (4.61%)	13/304 (4.28%)	16/303 (5.28%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
BASAL CELL CARCINOMA [A*]	5/304 (1.64%)	11/304 (3.62%)	15/304 (4.93%)	17/303 (5.61%)
Nervous system disorders				
HEADACHE [A*]	21/304 (6.91%)	14/304 (4.61%)	16/304 (5.26%)	15/303 (4.95%)
Respiratory, thoracic and mediastinal disorders				
COUGH [A*]	16/304 (5.26%)	13/304 (4.28%)	10/304 (3.29%)	13/303 (4.29%)
Vascular disorders				

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
HYPERTENSION A*	35/304 (11.51%)	30/304 (9.87%)	32/304 (10.53%)	33/303 (10.89%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, Medra Version 14.0

[1] Ocular Fellow Eye disorders

[2] Ocular Study Eye disorders

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Clinical Trials Administrator
Organization: Regeneron Pharmaceuticals
Phone:
Email: clinicaltrials@regeneron.com

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	○	○	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	◉	◉	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: December 17, 2012 (v17)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2012

Overall Status: Completed

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Actual]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Results First Submitted:	December 16, 2011
Results First Submitted that Met QC Criteria:	April 13, 2012
Results First Posted:	April 16, 2012 [Estimate]
Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	December 17, 2012
Last Update Posted:	December 20, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase 3, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.

Detailed Description:

Conditions

Conditions: Macular Degeneration

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Interventional Study Model: Parallel Assignment

Number of Arms: 4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1217 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: ranibizumab 0.5mg Q4	Biological: ranibizumab Participants received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • Lucentis

Arms	Assigned Interventions
Experimental: aflibercept injection 2.0mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 0.5mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 0.5mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 2.0mg Q8	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) of: letter score of 73 to 25 (20/40 to 20/320) in the study eye at 4 meters.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key

Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.

5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	The study was conducted at 164 sites in the United States and Canada. Recruitment period: 02 Aug 2007 to 15 Sep 2009.

Pre-assignment Details	2063 patients were screened, 1217 randomized, and 1215 included in the Safety Analysis Set (SAF). The Full Analysis Set (FAS) included 1210 patients with at least 1 post-baseline assessment. The Per Protocol Set (PPS) included 1089 patients who received ≥ 9 doses of study drug and attended ≥ 9 scheduled visits during the first year.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and received sham injections at interim monthly visits.

Overall Study

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
Started	306	304	304	303
Patients Received Treatment (SAF)	304	304	304	303
Full Analysis Set (FAS) Population	304	304	301	301
Per Protocol Set (PPS) Population	269	285	270	265
Completed	284	293	277	276
Not Completed	22	11	27	27
Adverse Event	4	3	5	4
Death	3	1	2	7
Lack of Efficacy	0	0	2	2
Lost to Follow-up	1	2	4	4
OTHER	1	0	4	1
Protocol Violation	3	0	3	1
Withdrawal by Subject	10	5	7	8

Baseline Characteristics

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

Baseline Measures

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants		304	304	304	303	1215
Age Continuous [1] Mean (Standard Deviation) Unit of measure: years	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
		78.2 (0 to 0)	77.7 (0 to 0)	78.3 (0 to 0)	77.9 (0 to 0)	78.0 (8.00)
		[1] Measure Description: SAF population used for analysis.				
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	Female	172 56.58%	194 63.82%	169 55.59%	179 59.08%	714 58.77%
	Male	132 43.42%	110 36.18%	135 44.41%	124 40.92%	501 41.23%
Ethnicity (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	Hispanic or Latino	7 2.3% (0 to 0)	11 3.62% (0 to 0)	11 3.62% (0 to 0)	12 3.96% (0 to 0)	41 3.37%
	Not Hispanic or Latino	297 97.7%	293 96.38%	293 96.38%	291 96.04%	1174 96.63%
	Unknown or Not Reported	0 0%	0 0%	0 0%	0 0%	0 0%
		[1] Measure Description: SAF population used for analysis.				

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Race (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	American Indian or Alaska Native	2 0.66% (0 to 0)	0 0% (0 to 0)	2 0.66% (0 to 0)	1 0.33% (0 to 0)	5 0.41%
	Asian	0 0% (0 to 0)	3 0.99% (0 to 0)	5 1.64% (0 to 0)	4 1.32% (0 to 0)	12 0.99%
	Native Hawaiian or Other Pacific Islander	1 0.33% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	2 0.16%
	Black or African American	1 0.33% (0 to 0)	1 0.33% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	3 0.25%
	White	296 97.37% (0 to 0)	295 97.04% (0 to 0)	294 96.71% (0 to 0)	289 95.38% (0 to 0)	1174 96.63%
	More than one race	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	1 0.08%
	Unknown or Not Reported	4 1.32% (0 to 0)	5 1.64% (0 to 0)	3 0.99% (0 to 0)	6 1.98% (0 to 0)	18 1.48%
		[1] Measure Description: SAF population used for analysis.				
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1] Mean (Standard Deviation)	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Unit of measure: scores on a scale		71.7 (0 to 0)	70.4 (0 to 0)	71.1 (0 to 0)	69.5 (0 to 0)	70.7 (17.11)
		[1] Measure Description: SAF population used for analysis. The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.				
Baseline Area of Choroidal Neovascularization (CNV) [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.52 (0 to 0)	6.59 (0 to 0)	6.49 (0 to 0)	6.56 (0 to 0)	6.54 (4.968)
		[1] Measure Description: SAF population used for analysis.				
Baseline Lesion Type [1] Measure type: Number Unit of measure: patients	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Occult		115 (0 to 0)	110 (0 to 0)	123 (0 to 0)	118 (0 to 0)	466 38.35%
Minimally Classic		101 (0 to 0)	105 (0 to 0)	97 (0 to 0)	112 (0 to 0)	415 34.16%
Predominantly Classic		82 (0 to 0)	87 (0 to 0)	82 (0 to 0)	71 (0 to 0)	322 26.5%
Missing		6 (0 to 0)	2 (0 to 0)	2 (0 to 0)	2 (0 to 0)	12 0.99%
		[1] Measure Description: SAF population used for analysis.				
Baseline Total Lesion Size [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.99 (0 to 0)	6.98 (0 to 0)	6.96 (0 to 0)	6.88 (0 to 0)	6.95 (5.202)

		Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
		[1] Measure Description: SAF population used for analysis.				
Baseline Best Corrected Visual Acuity (BCVA) [1] Mean (Standard Deviation) Unit of measure: letters read	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
		54.0 (0 to 0)	55.2 (0 to 0)	55.5 (0 to 0)	55.7 (0 to 0)	55.1 (13.14)
		[1] Measure Description: SAF population used for analysis. BCVA assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For BCVA tested via the 4 meter ETDRS protocol, 83 letters or more would represent 20/20 vision or better which would be considered an excellent outcome. Although, the ETDRS charts include 100 letters as the maximum possible score. The worst outcome is 0 letters read.				

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)
Measure Description	Defined "maintenance of vision" as patients who lost fewer than 15 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline.
Time Frame	Baseline and at week 52

Analysis Population Description

PPS population used for analysis.

Reporting Groups

	Description

Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	269	285	270	265	1089
Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF) Measure Type: Number Unit of Measure: percentage of patients	94.4 (0)	95.1 (0)	95.9 (0)	95.1 (0)	95.1 (0)

Statistical Analysis 1 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI.
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.4 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A positive value favors IAI 2.0Q4. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 2 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI (EYLEA, VEGF Trap-Eye).
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95.1% -5.1 to 2.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A negative value favors the IAI 0.5Q4 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 3 for Percentage of Patients Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of patients with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of patients with maintained vision for each of the groups treated with IAI (EYLEA, VEGF Trap-Eye).
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.5 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus IAI. A negative value favors the IAI 2.0Q8 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

2. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	8.1 (15.25)	10.9 (13.77)	6.9 (13.41)	7.9 (15.00)	8.5 (14.44)

Statistical Analysis 1 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0054
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	3.15
	Confidence Interval	(2-sided) 95.1% 0.92 to 5.37
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4793
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.80
	Confidence Interval	(2-sided) 95.1% -3.03 to 1.43
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8179
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares Means
	Estimated Value	0.26
	Confidence Interval	(2-sided) 95.1% -1.97 to 2.49
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q8.

3. Secondary Outcome Measure:

Measure Title	Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF. Measure Type: Number Unit of Measure: percentage of patients	30.9 (0)	37.5 (0)	24.9 (0)	30.6 (0)	31.1 (0)

Statistical Analysis 1 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1042
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	6.6
	Confidence Interval	(2-sided) 95.1% -1.0 to 14.1
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1037
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-6.0
	Confidence Interval	(2-sided) 95.1% -13.2 to 1.2
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Percentage of Patients Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.93
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.4
	Confidence Interval	(2-sided) 95.1% -7.7 to 7.0
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q8.

4. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.
Time Frame	Baseline and at Week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: scores on a scale	4.9 (14.01)	6.7 (13.50)	4.5 (11.87)	5.1 (14.74)	5.3 (13.59)

Statistical Analysis 1 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2090
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences Least Squares means
	Estimated Value	1.28
	Confidence Interval	(2-sided) 95.1% -0.73 to 3.28
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5128
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.67
	Confidence Interval	(2-sided) 95.1% -2.69 to 1.35
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5579
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.60
	Confidence Interval	(2-sided) 95.1% -2.61 to 1.42
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A positive value favors IAI 2.0Q8.

5. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)
Measure Description	CNV area values measured in square millimeters (mm^2); lower values represent better outcomes.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.

IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: mm^2	-4.2 (5.59)	-4.6 (5.47)	-3.5 (5.27)	-3.4 (6.02)	-3.9 (5.61)

Statistical Analysis 1 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3575
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.33
	Confidence Interval	(2-sided) 95.1% -1.04 to 0.38
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 2.0Q4

Statistical Analysis 2 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0507
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.71
	Confidence Interval	(2-sided) 95.1% -0.01 to 1.42
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 0.5Q4

Statistical Analysis 3 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0173
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.86
	Confidence Interval	(2-sided) 95.1% 0.15 to 1.58
	Estimation Comments	The difference is calculated as IAI minus ranibizumab. A negative value favors IAI 2.0Q8

Reported Adverse Events

Time Frame	AEs reported from Day 1 to Wk 96. Yr 1 of tx (Day 1 to Wk 52): 21-day screening period followed by administration of study drug every 4 or 8 wks including sham injections at interim study visits (when study drug was not administered) for 48 wks.
Adverse Event Reporting Description	Yr 2 of tx (Wk 52 to Wk 96): Pts evaluated every 4 wks and received IVT injections of study drug (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 wks.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Patients received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of ranibizumab (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.

IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	Patients received a 0.5mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 4 weeks for the first year. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.
IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8	Patients received a 2.0mg dose of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits. During the second year of treatment, patients were evaluated every 4 weeks and received IVT injections of Intravitreal Aflibercept Injection (IAI, EYLEA, VEGF Trap-Eye) (sham injections were not given) at intervals determined by specific re-treatment criteria. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks.

All-Cause Mortality

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/

Serious Adverse Events

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	94/304 (30.92%)	70/304 (23.03%)	88/304 (28.95%)	90/303 (29.7%)
Blood and lymphatic system disorders				
ANAEMIA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
COAGULOPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Congenital, familial and genetic disorders				

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ARTERIOVENOUS MALFORMATION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Ear and labyrinth disorders				
ACUTE CORONARY SYNDROME [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
ACUTE MYOCARDIAL INFARCTION [A*]	1/304 (0.33%)	2/304 (0.66%)	2/304 (0.66%)	1/303 (0.33%)
ANGINA UNSTABLE [A*]	3/304 (0.99%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
AORTIC VALVE STENOSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ARRHYTHMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ARTERIOSCLEROSIS CORONARY ARTERY [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ATRIAL FIBRILLATION [A*]	3/304 (0.99%)	2/304 (0.66%)	7/304 (2.3%)	7/303 (2.31%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BRADYCARDIA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CARDIAC ARREST [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
CARDIAC FAILURE ACUTE [A*]	1/304 (0.33%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
CARDIAC FAILURE CHRONIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CARDIAC FAILURE CONGESTIVE [A*]	4/304 (1.32%)	2/304 (0.66%)	4/304 (1.32%)	8/303 (2.64%)
CARDIO-RESPIRATORY ARREST [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CARDIOMYOPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CORONARY ARTERY DISEASE [A*]	5/304 (1.64%)	0/304 (0%)	6/304 (1.97%)	1/303 (0.33%)
CORONARY ARTERY OCCLUSION [A*]	1/304 (0.33%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
CORONARY ARTERY STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
INTRACARDIAC THROMBUS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MENIERE'S DISEASE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MITRAL VALVE INCOMPETENCE [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
MYOCARDIAL INFARCTION [A*]	6/304 (1.97%)	1/304 (0.33%)	5/304 (1.64%)	2/303 (0.66%)
MYOCARDIAL ISCHAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PERICARDIAL EFFUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SICK SINUS SYNDROME [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUPRAVENTRICULAR TACHYCARDIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TACHYARRHYTHMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
TACHYCARDIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
VENTRICULAR FIBRILLATION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VENTRICULAR TACHYCARDIA [A*]	0/304 (0%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
VERTIGO [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
Eye disorders				
AGE-RELATED MACULAR DEGENERATION [A [1]*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ANGLE CLOSURE GLAUCOMA [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BLEPHARITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BLINDNESS TRANSIENT [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CATARACT [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOROIDAL HAEMORRHAGE [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOROIDAL NEOVASCULARISATION [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONJUNCTIVAL HAEMORRHAGE [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONJUNCTIVITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DRY Eye disorders [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders IRRITATION [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders PAIN [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Eye disorders PRURITUS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOREIGN BODY SENSATION IN Eye disordersS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
KERATITIS [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LACRIMATION INCREASED [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MACULAR DEGENERATION [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MACULAR HOLE [A] [2]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MACULOPATHY [A] [1]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
POSTERIOR CAPSULE OPACIFICATION [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PSEUDOENDOPHTHALMITIS [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL DEGENERATION [A] [2]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RETINAL DETACHMENT [A] [1]*	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
RETINAL HAEMORRHAGE [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL OEDEMA [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL PIGMENT EPITHELIAL TEar and labyrinth disorders [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL PIGMENT EPITHELIOPATHY [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL TEar and labyrinth disorders [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
UVEITIS [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
VISION BLURRED [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VISUAL ACUITY REDUCED [A] [1]*	1/304 (0.33%)	1/304 (0.33%)	3/304 (0.99%)	0/303 (0%)
VITREOUS DETACHMENT [A] [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VITREOUS FLOATERS [A] [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
VITREOUS HAEMORRHAGE [A] [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Gastrointestinal disorders				
ABDOMINAL HERNIA [A]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ABDOMINAL HERNIA OBSTRUCTIVE [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
ASTHENIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CATHETER SITE HAEMATOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CHEST PAIN [A*]	2/304 (0.66%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
COLITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
COLITIS ISCHAEMIC [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
COLONIC POLYP [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONSTIPATION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DEATH [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
DEVICE DISLOCATION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
DIARRHOEA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DRUG WITHDRAWAL SYNDROME [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DUODENAL ULCER HAEMORRHAGE [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DYSPHAGIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOOD POISONING [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
GASTRIC HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTRIC ULCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS EROSIVE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
GASTROINTESTINAL DISORDER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
GASTROINTESTINAL MOTILITY DISORDER [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROINTESTINAL OBSTRUCTION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
GASTROOESOPHAGEAL REFLUX DISEASE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMATOCHEZIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMORRHOIDS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HIATUS HERNIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ILEUS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
INGUINAL HERNIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INTESTINAL OBSTRUCTION [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
LOWER GASTROINTESTINAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
NAUSEA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
NON-CARDIAC CHEST PAIN [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
OESOPHAGEAL ULCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PANCREATITIS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
PYREXIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SMALL INTESTINAL OBSTRUCTION [A*]	2/304 (0.66%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
Hepatobiliary disorders				
BILE DUCT STONE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CHOLANGITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHOLECYSTITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
CHOLECYSTITIS ACUTE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOLECYSTITIS CHRONIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHOLELITHIASIS [A*]	1/304 (0.33%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
PORTAL HYPERTENSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PORTAL VEIN THROMBOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Immune system disorders				
DRUG HYPERSENSITIVITY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Infections and infestations				
ANAL ABSCESS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ANORECTAL CELLULITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ARTHRITIS BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
BACTERIAL DISEASE CARRIER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BRONCHITIS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	3/303 (0.99%)
CELLULITIS [A*]	3/304 (0.99%)	3/304 (0.99%)	2/304 (0.66%)	0/303 (0%)
CLOSTRIDIAL Infections and infestationsION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
CLOSTRIDIUM DIFFICILE COLITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DEVICE RELATED Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
DIVERTICULITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
ENCEPHALITIS VIRAL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOCARDITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOPHTHALMITIS [A [1]*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ESCHERICHIA URINARY TRACT Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROENTERITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
GASTROENTERITIS VIRAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
INFLUENZA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
KLEBSIELLA BACTERAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LABYRINTHITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LOBAR PNEUMONIA [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
LUNG Infections and infestationsION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
NASOPHARYNGITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PHARYNGITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PNEUMONIA [A*]	14/304 (4.61%)	6/304 (1.97%)	5/304 (1.64%)	8/303 (2.64%)
PYELONEPHRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SCROTAL ABSCESS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SEPSIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SEPTIC SHOCK [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SINUSITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SINUSITIS FUNGAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
STAPHYLOCOCCAL BACTERAEMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
UPPER RESPIRATORY TRACT Infections and infestationsION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
URINARY TRACT Infections and infestationsION [A*]	1/304 (0.33%)	3/304 (0.99%)	0/304 (0%)	0/303 (0%)
URINARY TRACT Infections and infestationsION BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
URINARY TRACT Infections and infestationsION STAPHYLOCOCCAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
UROSEPSIS [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
VESTIBULAR NEURONITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL Infections and infestationsION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL PERICARDITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
WOUND Infections and infestationsION BACTERIAL [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Injury, poisoning and procedural complications				
ACCIDENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CERVICAL VERTEBRAL FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONCUSSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
FALL [A*]	8/304 (2.63%)	13/304 (4.28%)	7/304 (2.3%)	16/303 (5.28%)
FEMORAL NECK FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
FEMUR FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	2/303 (0.66%)
FIBULA FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
FOOT FRACTURE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
HEAD Injury, poisoning and procedural complications [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HIP FRACTURE [A*]	1/304 (0.33%)	4/304 (1.32%)	2/304 (0.66%)	1/303 (0.33%)
HUMERUS FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	3/304 (0.99%)	0/303 (0%)
INCISIONAL HERNIA, OBSTRUCTIVE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INCORRECT DOSE ADMINISTERED [A [2]*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
JOINT DISLOCATION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
JOINT Injury, poisoning and procedural complications [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LUMBAR VERTEBRAL FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MENISCUS LESION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
POST LAMINECTOMY SYNDROME [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PROCEDURAL PAIN [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PUBIS FRACTURE [A*]	1/304 (0.33%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
RIB FRACTURE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
ROAD TRAFFIC ACCIDENT [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SNAKE BITE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SPINAL COMPRESSION FRACTURE [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
SPINAL FRACTURE [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
STERNAL FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SUBCUTANEOUS HAEMATOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUBDURAL HAEMATOMA [A*]	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
TIBIA FRACTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
TRAUMATIC BRAIN Injury, poisoning and procedural complications [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
UPPER LIMB FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
VASCULAR PSEUDOANEURYSM [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Investigations				
Blood and lymphatic system disorders GLUCOSE INCREASED [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Blood and lymphatic system disorders PRESSURE INCREASED [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
Blood and lymphatic system disorders PRESSURE ORTHOSTATIC ABNORMAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
INTRAOCULAR PRESSURE INCREASED [A [1]*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Metabolism and nutrition disorders				
DEHYDRATION [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
DIABETES MELLITUS [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
DIABETES MELLITUS INADEQUATE CONTROL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ELECTROLYTE IMBALANCE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPERKALAEMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HYPOGLYCAEMIA [A*]	0/304 (0%)	2/304 (0.66%)	1/304 (0.33%)	0/303 (0%)
HYPOKALAEMIA [A*]	2/304 (0.66%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPONATRAEMIA [A*]	2/304 (0.66%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
MALNUTRITION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HYPOGLYCAEMIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Musculoskeletal and connective tissue disorders				
ARTHRALGIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ARTHRITIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
ARTHROPATHY [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BACK PAIN [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CERVICAL SPINAL STENOSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
INTERVERTEBRAL DISC DEGENERATION [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
INTERVERTEBRAL DISC PROTRUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUMBAR SPINAL STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
OSTEOARTHRITIS [A*]	4/304 (1.32%)	1/304 (0.33%)	3/304 (0.99%)	1/303 (0.33%)
OSTEONECROSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PAIN IN EXTREMITY [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RHABDOMYOLYSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SPINAL COLUMN STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPINAL OSTEOARTHRITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPONDYLOLISTHESIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
ATYPICAL FIBROXANTHOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
B-CELL LYMPHOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BASAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BLADDER TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	2/304 (0.66%)	1/303 (0.33%)
BLADDER TRANSITIONAL CELL CARCINOMA RECURRENT [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BRAIN NEOPLASM [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
BREAST Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	2/303 (0.66%)
BREAST Neoplasms benign, malignant and unspecified (incl cysts and polyps) IN SITU [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
BRONCHIOLOALVEOLAR CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CARDIAC MYXOMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CHRONIC LYMPHOCYTIC LEUKAEMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
COLON Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
COLON Neoplasms benign, malignant and unspecified (incl cysts and polyps) RECURRENT [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOMETRIAL Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
HEPATIC NEOPLASM MALIGNANT [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HEPATIC Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LEUKAEMIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
LUNG NEOPLASM [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUNG NEOPLASM MALIGNANT [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
LUNG SQUAMOUS CELL CARCINOMA STAGE II [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MALIGNANT MELANOMA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTASES TO CENTRAL NERVOUS SYSTEM [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
METASTASES TO Hepatobiliary disorders [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTASES TO LUNG [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
METASTASES TO LYMPH NODES [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
METASTATIC NEOPLASM [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
NEOPLASM MALIGNANT [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
NON-SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
NON-SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) STAGE IV [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
OESOPHAGEAL ADENOCARCINOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
PROSTATE Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	1/304 (0.33%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
PROSTATE Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
RECTAL Neoplasms benign, malignant and unspecified (incl cysts and polyps) STAGE III [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
RECTOSIGMOID Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RENAL CELL CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
SALIVARY GLAND Neoplasms benign, malignant and unspecified (incl cysts and polyps) RECURRENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SMALL CELL LUNG Neoplasms benign, malignant and unspecified (incl cysts and polyps) METASTATIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SMALL CELL LUNG Neoplasms benign,malignant & unspecified(incl cysts and polyps)STAGE UNSPECIFIED [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SQUAMOUS CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SQUAMOUS CELL CARCINOMA OF Skin and subcutaneous tissue disorders [A*]	5/304 (1.64%)	3/304 (0.99%)	2/304 (0.66%)	4/303 (1.32%)
THYROID Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TONSIL Neoplasms benign, malignant and unspecified (incl cysts and polyps) [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TUMOUR HAEMORRHAGE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
WALDENSTROM'S MACROGLOBULINAEMIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Nervous system disorders				
APHASIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BALANCE DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CAROTID ARTERY DISEASE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CAROTID ARTERY STENOSIS [A*]	0/304 (0%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
CEREBELLAR INFARCTION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CEREBRAL ARTERY THROMBOSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CEREBRAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBRAL INFARCTION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBROVASCULAR ACCIDENT [A*]	2/304 (0.66%)	3/304 (0.99%)	1/304 (0.33%)	5/303 (1.65%)
COMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONVULSION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DEMENTIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DIZZINESS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
EMBOLIC STROKE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HEADACHE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ISCHAEMIC CEREBRAL INFARCTION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LACUNAR INFARCTION [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LOSS OF CONSCIOUSNESS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
METABOLIC ENCEPHALOPATHY [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PRESYNCOPE [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
SPINAL CORD COMPRESSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SUBARACHNOID HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
SYNCOPE [A*]	3/304 (0.99%)	1/304 (0.33%)	3/304 (0.99%)	1/303 (0.33%)
TRANSIENT GLOBAL AMNESIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
TRANSIENT ISCHAEMIC ATTACK [A*]	0/304 (0%)	3/304 (0.99%)	7/304 (2.3%)	5/303 (1.65%)
Psychiatric disorders				
CONFUSIONAL STATE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MENTAL STATUS CHANGES [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Psychiatric disordersOTIC DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Renal and urinary disorders				
CALCULUS BLADDER [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CALCULUS URETERIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HAEMATURIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HYDRONEPHROSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RENAL FAILURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RENAL FAILURE ACUTE [A*]	0/304 (0%)	3/304 (0.99%)	2/304 (0.66%)	2/303 (0.66%)
RENAL FAILURE CHRONIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Reproductive system and breast disorders				
CYSTOCELE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RECTOCELE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Respiratory, thoracic and mediastinal disorders				
ACUTE RESPIRATORY FAILURE [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
APNOEIC ATTACK [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ASTHMA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
CHRONIC OBSTRUCTIVE PULMONARY DISEASE [A*]	3/304 (0.99%)	3/304 (0.99%)	6/304 (1.97%)	6/303 (1.98%)
COUGH [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
DYSPNOEA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
EMPHYSEMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PLEURAL EFFUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PNEUMONIA ASPIRATION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
PNEUMONITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
PULMONARY EMBOLISM [A*]	0/304 (0%)	2/304 (0.66%)	1/304 (0.33%)	2/303 (0.66%)
PULMONARY FIBROSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PULMONARY MASS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PULMONARY OEDEMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RESPIRATORY DISTRESS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RESPIRATORY FAILURE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RESTRICTIVE PULMONARY DISEASE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TRACHEAL MASS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Skin and subcutaneous tissue disorders				
ANGIOEDEMA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
Surgical and medical procedures				
CHOLECYSTECTOMY [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
MICROGRAPHIC Skin and subcutaneous tissue disorders SURGERY [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
Vascular disorders				
AORTIC ANEURYSM [A*]	1/304 (0.33%)	2/304 (0.66%)	1/304 (0.33%)	0/303 (0%)
AORTIC ANEURYSM RUPTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
AORTIC STENOSIS [A*]	1/304 (0.33%)	1/304 (0.33%)	2/304 (0.66%)	1/303 (0.33%)
ARTERIOSCLEROSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DEEP VEIN THROMBOSIS [A*]	1/304 (0.33%)	1/304 (0.33%)	1/304 (0.33%)	2/303 (0.66%)
FEMORAL ARTERY ANEURYSM [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HAEMATOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPERTENSION [A*]	2/304 (0.66%)	0/304 (0%)	3/304 (0.99%)	0/303 (0%)
HYPOTENSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ILIAC ARTERY OCCLUSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
LYMPHATIC FISTULA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LYMPHOCELE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ORTHOSTATIC HYPOTENSION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PERIPHERAL ARTERY ANEURYSM [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PERIPHERAL VASCULAR DISORDER [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PHLEBITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
PHLEBITIS DEEP A*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HAEMORRHAGIC A*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, Medra Version 14.0

[1] Ocular Fellow Eye disorders

[2] Ocular Study Eye disorders

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	261/304 (85.86%)	254/304 (83.55%)	262/304 (86.18%)	258/303 (85.15%)
Ear and labyrinth disorders				
ATRIOVENTRICULAR BLOCK FIRST DEGREE A*	16/304 (5.26%)	18/304 (5.92%)	8/304 (2.63%)	9/303 (2.97%)
Eye disorders				
AGE-RELATED MACULAR DEGENERATION A [1]*	21/304 (6.91%)	16/304 (5.26%)	12/304 (3.95%)	15/303 (4.95%)
BLEPHARITIS A [1]*	16/304 (5.26%)	18/304 (5.92%)	14/304 (4.61%)	14/303 (4.62%)
CATARACT A [1]*	10/304 (3.29%)	17/304 (5.59%)	10/304 (3.29%)	10/303 (3.3%)
CHOROIDAL NEOVASCULARISATION A [1]*	17/304 (5.59%)	10/304 (3.29%)	13/304 (4.28%)	9/303 (2.97%)
CONJUNCTIVAL HAEMORRHAGE A [1]*	16/304 (5.26%)	17/304 (5.59%)	16/304 (5.26%)	19/303 (6.27%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
DRY Eye disorders [A] [2]*	12/304 (3.95%)	16/304 (5.26%)	10/304 (3.29%)	14/303 (4.62%)
Eye disorders IRRITATION [A] [2]*	19/304 (6.25%)	13/304 (4.28%)	15/304 (4.93%)	16/303 (5.28%)
Eye disorders PAIN [A] [2]*	34/304 (11.18%)	39/304 (12.83%)	35/304 (11.51%)	31/303 (10.23%)
Eye disorders PRURITUS [A] [2]*	11/304 (3.62%)	16/304 (5.26%)	10/304 (3.29%)	6/303 (1.98%)
FOREIGN BODY SENSATION IN Eye disordersS [A] [2]*	9/304 (2.96%)	10/304 (3.29%)	10/304 (3.29%)	19/303 (6.27%)
LACRIMATION INCREASED [A] [2]*	11/304 (3.62%)	11/304 (3.62%)	15/304 (4.93%)	16/303 (5.28%)
MACULAR DEGENERATION [A] [1]*	22/304 (7.24%)	14/304 (4.61%)	21/304 (6.91%)	14/303 (4.62%)
RETINAL HAEMORRHAGE [A] [1]*	43/304 (14.14%)	36/304 (11.84%)	36/304 (11.84%)	22/303 (7.26%)
RETINAL OEDEMA [A] [1]*	18/304 (5.92%)	8/304 (2.63%)	12/304 (3.95%)	11/303 (3.63%)
RETINAL PIGMENT EPITHELIOPATHY [A] [2]*	14/304 (4.61%)	18/304 (5.92%)	17/304 (5.59%)	14/303 (4.62%)
VISION BLURRED [A] [2]*	12/304 (3.95%)	18/304 (5.92%)	17/304 (5.59%)	13/303 (4.29%)
VISUAL ACUITY REDUCED [A] [1]*	27/304 (8.88%)	10/304 (3.29%)	20/304 (6.58%)	19/303 (6.27%)
VITREOUS DETACHMENT [A] [1]*	16/304 (5.26%)	24/304 (7.89%)	25/304 (8.22%)	24/303 (7.92%)
VITREOUS FLOATERS [A] [2]*	47/304 (15.46%)	49/304 (16.12%)	30/304 (9.87%)	29/303 (9.57%)
Gastrointestinal disorders				
DIARRHOEA [A]*	18/304 (5.92%)	18/304 (5.92%)	8/304 (2.63%)	9/303 (2.97%)
NAUSEA [A]*	15/304 (4.93%)	16/304 (5.26%)	15/304 (4.93%)	15/303 (4.95%)
Infections and infestations				
BRONCHITIS [A]*	23/304 (7.57%)	19/304 (6.25%)	16/304 (5.26%)	24/303 (7.92%)
NASOPHARYNGITIS [A]*	36/304 (11.84%)	46/304 (15.13%)	41/304 (13.49%)	39/303 (12.87%)

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
SINUSITIS [A*]	18/304 (5.92%)	13/304 (4.28%)	17/304 (5.59%)	14/303 (4.62%)
UPPER RESPIRATORY TRACT Infections and infestationsION [A*]	18/304 (5.92%)	18/304 (5.92%)	19/304 (6.25%)	26/303 (8.58%)
URINARY TRACT Infections and infestationsION [A*]	26/304 (8.55%)	22/304 (7.24%)	25/304 (8.22%)	23/303 (7.59%)
Injury, poisoning and procedural complications				
FALL [A*]	19/304 (6.25%)	13/304 (4.28%)	15/304 (4.93%)	21/303 (6.93%)
Investigations				
Blood and lymphatic system disorders GLUCOSE INCREASED [A*]	13/304 (4.28%)	12/304 (3.95%)	17/304 (5.59%)	16/303 (5.28%)
INTRAOCULAR PRESSURE INCREASED [A [1]*]	16/304 (5.26%)	8/304 (2.63%)	15/304 (4.93%)	15/303 (4.95%)
Musculoskeletal and connective tissue disorders				
ARTHRALGIA [A*]	17/304 (5.59%)	18/304 (5.92%)	17/304 (5.59%)	8/303 (2.64%)
BACK PAIN [A*]	11/304 (3.62%)	14/304 (4.61%)	13/304 (4.28%)	16/303 (5.28%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
BASAL CELL CARCINOMA [A*]	5/304 (1.64%)	11/304 (3.62%)	15/304 (4.93%)	17/303 (5.61%)
Nervous system disorders				
HEADACHE [A*]	21/304 (6.91%)	14/304 (4.61%)	16/304 (5.26%)	15/303 (4.95%)
Respiratory, thoracic and mediastinal disorders				
COUGH [A*]	16/304 (5.26%)	13/304 (4.28%)	10/304 (3.29%)	13/303 (4.29%)
Vascular disorders				

	Ranibizumab 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q4	IAI (EYLEA, VEGF Trap-Eye) 0.5mg Q4	IAI (EYLEA, VEGF Trap-Eye) 2.0mg Q8
HYPERTENSION A*	35/304 (11.51%)	30/304 (9.87%)	32/304 (10.53%)	33/303 (10.89%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, Medra Version 14.0

[1] Ocular Fellow Eye disorders

[2] Ocular Study Eye disorders

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Clinical Trials Administrator
Organization: Regeneron Pharmaceuticals
Phone:
Email: clinicaltrials@regeneron.com

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version (submitted December 20, 2012) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	July 31, 2007	None (earliest Version on record)
2	○	○	August 17, 2007	Recruitment Status, Study Status and Contacts/Locations

Version	A	B	Submitted Date	Changes
3	○	○	November 14, 2007	Contacts/Locations and Study Status
4	○	○	December 4, 2007	Study Status and Contacts/Locations
5	○	○	March 13, 2008	Study Status and Eligibility
6	○	○	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	○	○	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	○	○	March 3, 2009	Study Status and Contacts/Locations
9	○	○	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification
10	○	○	September 12, 2009	Recruitment Status, Study Status and Contacts/Locations
11	○	○	December 1, 2009	Study Status, Contacts/Locations and Sponsor/Collaborators
12	○	○	January 5, 2011	Study Status
13	○	○	April 18, 2011	Study Status, Study Design
14	○	○	May 4, 2011	Study Status
15	○	○	December 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators
16	◉	◉	April 13, 2012	Arms and Interventions, Outcome Measures, Study Status, More Information, Reported Adverse Events, Baseline Characteristics, Participant Flow, Eligibility, Study Description and Study Identification
17	○	○	December 17, 2012	Reported Adverse Events, Outcome Measures, Baseline Characteristics, Participant Flow, More Information and Study Status
18	○	○	December 20, 2012	More Information, Outcome Measures, References and Study Status

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00509795

Submitted Date: April 13, 2012 (v16)

Study Identification

Unique Protocol ID: VGFT-OD-0605

Brief Title: Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Official Title: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: April 2012

Overall Status: Completed

Study Start: August 2007

Primary Completion: September 2010 [Actual]

Study Completion: July 2011 [Actual]

First Submitted: July 31, 2007

First Submitted that Met QC Criteria: July 31, 2007

First Posted: August 1, 2007 [Estimate]

Results First Submitted:	December 16, 2011
Results First Submitted that Met QC Criteria:	April 13, 2012
Results First Posted:	April 16, 2012 [Estimate]
Certification/Extension First Submitted:	January 5, 2011
Certification/Extension First Submitted that Met QC Criteria:	January 5, 2011
Certification/Extension First Posted:	January 10, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	April 13, 2012
Last Update Posted:	April 16, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary:	This study is a phase 3, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.

Detailed Description:

Conditions

Conditions: Macular Degeneration

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Interventional Study Model: Parallel Assignment

Number of Arms: 4

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Allocation: Randomized

Enrollment: 1217 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: ranibizumab 0.5mg Q4	Biological: ranibizumab Participants received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • Lucentis

Arms	Assigned Interventions
Experimental: aflibercept injection 2.0mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 0.5mg Q4	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 0.5mg dose of aflibercept injection every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321
Experimental: aflibercept injection 2.0mg Q8	Biological: aflibercept injection (VEGF Trap-Eye, BAY86-5321) Participants received a 2.0mg dose of aflibercept injection every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. Other Names: • VEGF Trap-Eye • BAY86-5321

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

1. Signed Informed Consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) of: letter score of 73 to 25 (20/40 to 20/320) in the study eye at 4 meters.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key

Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.

5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
6. Scar or fibrosis, making up > 50% of total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina,other than AMD, in either eye.
12. Prior vitrectomy in the study eye.
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
14. Any history of macular hole of stage 2 and above in the study eye.
15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Alabama**

Birmingham, Alabama, United States, 35205

Birmingham, Alabama, United States, 35223

United States, Arizona

Phoenix, Arizona, United States, 85014

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

Tucson, Arizona, United States, 85710

United States, California

Beverly Hills, California, United States, 90211

Campbell, California, United States, 95008

Fullerton, California, United States, 92835

Glendale, California, United States, 91203

Irvine, California, United States, 92697

La Jolla, California, United States, 92037

Loma Linda, California, United States, 92354

Los Angeles, California, United States, 90033

Los Angeles, California, United States, 90048

Menlo Park, California, United States, 94025

Mountain View, California, United States, 94040

Oakland, California, United States, 94609

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Sacramento, California, United States, 95819

San Diego, California, United States, 92120

San Francisco, California, United States, 94107

Santa Ana, California, United States, 92705

Torrance, California, United States, 90503

Ventura, California, United States, 93003

Westlake Village, California, United States, 91361

Yorba Linda, California, United States, 92887

United States, Colorado

Aurora, Colorado, United States, 80045

Denver, Colorado, United States, 80205

Denver, Colorado, United States, 80230

United States, Connecticut

Bridgeport, Connecticut, United States, 06606

Hamden, Connecticut, United States, 06518

New Haven, Connecticut, United States, 06510

New London, Connecticut, United States, 06320

United States, Florida

Altamonte Springs, Florida, United States, 32701

Boynton Beach, Florida, United States, 33426

Fort Myers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33351

Ft. Myers, Florida, United States, 33912

Gainesville, Florida, United States, 32610

Jacksonville, Florida, United States, 32224

Miami, Florida, United States, 33136

Miami, Florida, United States, 33143

Mount Dora, Florida, United States, 32757

Orlando, Florida, United States, 32803

Orlando, Florida, United States, 32806

Oscala, Florida, United States, 34472

Palm Beach Gardens, Florida, United States, 33410

Pensacola, Florida, United States, 32503

Sarasota, Florida, United States

Stuart, Florida, United States, 34994

Tampa, Florida, United States, 33612

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Hawaii

Aiea, Hawaii, United States, 96701

Honolulu, Hawaii, United States, 96813

United States, Illinois

Oak Brook, Illinois, United States, 60523

United States, Indiana

Fort Wayne, Indiana, United States, 46804

Indianapolis, Indiana, United States, 46202

Indianapolis, Indiana, United States, 46260

Indianapolis, Indiana, United States, 46280

New Albany, Indiana, United States, 47150

United States, Iowa

Iowa City, Iowa, United States, 52242-1091

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Kentucky

Louisville, Kentucky, United States, 40202

Louisville, Kentucky, United States, 40207

Paducah, Kentucky, United States, 42001

United States, Louisiana

New Orleans, Louisiana, United States, 70115

New Orleans, Louisiana, United States, 70121

Shreveport, Louisiana, United States, 71105

United States, Maine

Bangor, Maine, United States, 04401

Portland, Maine, United States, 04102

United States, Maryland

Baltimore, Maryland, United States, 21209

Baltimore, Maryland, United States, 21287

Chevy Chase, Maryland, United States, 20815

Hagerstown, Maryland, United States, 21740

Towson, Maryland, United States, 21204

United States, Massachusetts

Boston, Massachusetts, United States, 02111

Boston, Massachusetts, United States, 02114

Boston, Massachusetts, United States, 02215

Boston, Massachusetts, United States

Peabody, Massachusetts, United States, 01960

United States, Michigan

Ann Arbor, Michigan, United States, 48105

Battle Creek, Michigan, United States, 49015

Detroit, Michigan, United States, 48202

Grand Rapids, Michigan, United States, 49525

Jackson, Michigan, United States, 49201

Royal Oak, Michigan, United States, 48073

Southfield, Michigan, United States, 48034

West Bloomfield, Michigan, United States, 48322

United States, Minnesota

Edina, Minnesota, United States, 55435

Minneapolis, Minnesota, United States, 55404

Rochester, Minnesota, United States, 55905

United States, Missouri

Florissant, Missouri, United States, 63031

Kansas City, Missouri, United States, 64108

Kansas City, Missouri, United States, 64111

Springfield, Missouri, United States, 65804

St. Louis, Missouri, United States, 63110

United States, Montana

Missoula, Montana, United States, 59801

United States, Nebraska

Lincoln, Nebraska, United States, 68506

Omaha, Nebraska, United States, 68131

United States, Nevada

Las Vegas, Nevada, United States, 89144

United States, New Jersey

Lawrenceville, New Jersey, United States, 08648

New Brunswick, New Jersey, United States, 08901

Northfield, New Jersey, United States, 08225

Teaneck, New Jersey, United States, 07666

Toms River, New Jersey, United States, 08753

United States, New Mexico

Albuquerque, New Mexico, United States, 87106

United States, New York

Albany, New York, United States, 12206

Brooklyn, New York, United States, 11223

Lynbrook, New York, United States, 11563

New York, New York, United States, 10003

New York, New York, United States, 10021

New York, New York, United States, 10032

Poughkeepsie, New York, United States, 12601

Rochester, New York, United States, 14620

Rochester, New York, United States, 14642

Slingerlands, New York, United States, 12159

Syracuse, New York, United States, 13224

United States, North Carolina

Asheville, North Carolina, United States, 28803

Charlotte, North Carolina, United States, 28210

Raleigh, North Carolina, United States, 27607

Southern Pines, North Carolina, United States, 28387

Winston-Salem, North Carolina, United States, 27157

United States, Ohio

Cincinnati, Ohio, United States, 45202

Cincinnati, Ohio, United States, 45242

Columbus, Ohio, United States, 43215

Toledo, Ohio, United States, 43608

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Ashland, Oregon, United States, 97520

Portland, Oregon, United States, 97210

Portland, Oregon, United States, 97227

Salem, Oregon, United States, 97302

United States, Pennsylvania

Kingston, Pennsylvania, United States, 18704

Philadelphia, Pennsylvania, United States, 19104

Philadelphia, Pennsylvania, United States, 19107

Philadelphia, Pennsylvania, United States, 19124

Pittsberg, Pennsylvania, United States, 15231

Pittsburgh, Pennsylvania, United States, 15212

Pittsburgh, Pennsylvania, United States, 15213

West Mifflin, Pennsylvania, United States, 15122

Wyomissing, Pennsylvania, United States, 19610

United States, Rhode Island

Providence, Rhode Island, United States, 02903-4928

United States, South Carolina

Charleston, South Carolina, United States, 29414

Columbia, South Carolina, United States, 29223

Greenville, South Carolina, United States, 29605

West Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Memphis, Tennessee, United States, 38119

Memphis, Tennessee, United States, 38120

Nashville, Tennessee, United States, 37203

United States, Texas

Abilene, Texas, United States, 79606

Austin, Texas, United States, 78705

Corpus Cristi, Texas, United States, 78413

Dallas, Texas, United States, 75390

DeSoto, Texas, United States, 75115

Ft. Worth, Texas, United States, 76102

Ft. Worth, Texas, United States, 76104

Galveston, Texas, United States, 77555

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

Odessa, Texas, United States, 79761

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

Salt Lake City, Utah, United States, 84132

United States, Vermont

Burlington, Vermont, United States, 05401

United States, Virginia

Charlottesville, Virginia, United States, 22908

Fairfax, Virginia, United States, 22031

Richmond, Virginia, United States, 23221

United States, Washington

Seattle, Washington, United States, 98104

Silverdale, Washington, United States, 98383

United States, Wisconsin

Madison, Wisconsin, United States, 53715

Madison, Wisconsin, United States, 58705

Milwaukee, Wisconsin, United States, 53226

Canada, Alberta

Calgary, Alberta, Canada, T3E 7MB

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 3N9

Victoria, British Columbia, Canada, V8V 1B3

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

London, Ontario, Canada, N6A 4G5

Mississauga, Ontario, Canada, L4W 1W9

Ottawa, Ontario, Canada, K1H8L6

Toronto, Ontario, Canada, M4N3M5

Toronto, Ontario, Canada, M5C 2T2

Canada, Quebec

Montreal, Quebec, Canada, H1T 2M4

Montreal, Quebec, Canada, H3A 1A1

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 1A5

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	The study was conducted at 164 sites in the United States and Canada. Recruitment period: 02 Aug 2007 to 15 Sep 2009.

Pre-assignment Details	2063 participants were screened, 1217 randomized, and 1215 included in the Safety Analysis Set (SAF). The Full Analysis Set (FAS) included 1210 participants with at least 1 post-baseline assessment. The Per Protocol Set (PPS) included 1089 participants who received ≥ 9 doses of study drug and attended ≥ 9 scheduled visits during the first year.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

Overall Study

	Ranibizumab 0.5mg Q4	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg Q4	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 0.5mg Q4	Aflibercept Injection (VEGF Trap-Eye, BAY86-5321) 2.0mg Q8
Started	306	304	304	303
Participants Received Treatment (SAF)	304	304	304	303
Full Analysis Set (FAS) Population	304	304	301	301
Per Protocol Set (PPS) Population	269	285	270	265
Completed	284	293	277	276
Not Completed	22	11	27	27
Adverse Event	4	3	5	4
Death	3	1	2	7
Lack of Efficacy	0	0	2	2
Lost to Follow-up	1	2	4	4
OTHER	1	0	4	1
Protocol Violation	3	0	3	1
Withdrawal by Subject	10	5	7	8

Baseline Characteristics

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.

Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

Baseline Measures

		Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants		304	304	304	303	1215
Age Continuous [1] Mean (Standard Deviation) Unit of measure: years	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
		78.2 (0 to 0)	77.7 (0 to 0)	78.3 (0 to 0)	77.9 (0 to 0)	78.0 (8.00)
		[1] Measure Description: SAF population used for analysis.				
Sex: Female, Male [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	Female	172 56.58% (0 to 0)	194 63.82% (0 to 0)	169 55.59% (0 to 0)	179 59.08% (0 to 0)	714 58.77%
	Male	132 43.42% (0 to 0)	110 36.18% (0 to 0)	135 44.41% (0 to 0)	124 40.92% (0 to 0)	501 41.23%
		[1] Measure Description: SAF population used for analysis.				
Ethnicity (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants

		Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
	Hispanic or Latino	7 2.3% (0 to 0)	11 3.62% (0 to 0)	11 3.62% (0 to 0)	12 3.96% (0 to 0)	41 3.37%
	Not Hispanic or Latino	297 97.7% (0 to 0)	293 96.38% (0 to 0)	293 96.38% (0 to 0)	291 96.04% (0 to 0)	1174 96.63%
	Unknown or Not Reported	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	0 0%
		[1] Measure Description: SAF population used for analysis.				
Race (NIH/OMB) [1] Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
	American Indian or Alaska Native	2 0.66% (0 to 0)	0 0% (0 to 0)	2 0.66% (0 to 0)	1 0.33% (0 to 0)	5 0.41%
	Asian	0 0% (0 to 0)	3 0.99% (0 to 0)	5 1.64% (0 to 0)	4 1.32% (0 to 0)	12 0.99%
	Native Hawaiian or Other Pacific Islander	1 0.33% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	2 0.16%
	Black or African American	1 0.33% (0 to 0)	1 0.33% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	3 0.25%
	White	296 97.37% (0 to 0)	295 97.04% (0 to 0)	294 96.71% (0 to 0)	289 95.38% (0 to 0)	1174 96.63%
	More than one race	0 0% (0 to 0)	0 0% (0 to 0)	0 0% (0 to 0)	1 0.33% (0 to 0)	1 0.08%

		Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
	Unknown or Not Reported	4 1.32% (0 to 0)	5 1.64% (0 to 0)	3 0.99% (0 to 0)	6 1.98% (0 to 0)	18 1.48%
		[1] Measure Description: SAF population used for analysis.				
Baseline National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: scores on a scale		71.7 (0 to 0)	70.4 (0 to 0)	71.1 (0 to 0)	69.5 (0 to 0)	70.7 (17.11)
		[1] Measure Description: SAF population used for analysis. The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.				
Baseline Area of Choroidal Neovascularization (CNV) [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.52 (0 to 0)	6.59 (0 to 0)	6.49 (0 to 0)	6.56 (0 to 0)	6.54 (4.968)
		[1] Measure Description: SAF population used for analysis.				
Baseline Lesion Type [1] Measure type: Number Unit of measure: participants	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Occult		115 (0 to 0)	110 (0 to 0)	123 (0 to 0)	118 (0 to 0)	466 38.35%

		Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Minimally Classic		101 (0 to 0)	105 (0 to 0)	97 (0 to 0)	112 (0 to 0)	415 34.16%
Predominantly Classic		82 (0 to 0)	87 (0 to 0)	82 (0 to 0)	71 (0 to 0)	322 26.5%
Missing		6 (0 to 0)	2 (0 to 0)	2 (0 to 0)	2 (0 to 0)	12 0.99%
		[1] Measure Description: SAF population used for analysis.				
Baseline Total Lesion Size [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: mm^2		6.99 (0 to 0)	6.98 (0 to 0)	6.96 (0 to 0)	6.88 (0 to 0)	6.95 (5.202)
		[1] Measure Description: SAF population used for analysis.				
Baseline Best Corrected Visual Acuity (BCVA) [1]	Number Analyzed	304 Participants	304 Participants	304 Participants	303 Participants	1215 Participants
Mean (Standard Deviation) Unit of measure: letters read		54.0 (0 to 0)	55.2 (0 to 0)	55.5 (0 to 0)	55.7 (0 to 0)	55.1 (13.14)
		[1] Measure Description: SAF population used for analysis. BCVA assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For BCVA tested via the 4 meter ETDRS protocol, 83 letters or more would represent 20/20 vision or better which would be considered an excellent outcome. Although, the ETDRS charts include 100 letters as the maximum possible score. The worst outcome is 0 letters read.				

Outcome Measures

1. Primary Outcome Measure:

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1841 of 2000

Measure Title	Percentage of Participants Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)
Measure Description	Defined "maintenance of vision" as subjects who lost fewer than 15 letters in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline.
Time Frame	Baseline and at week 52

Analysis Population Description

PPS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants Analyzed	269	285	270	265	1089
Percentage of Participants Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF) Measure Type: Number Unit of Measure: percentage of participants	94.4 (0)	95.1 (0)	95.9 (0)	95.1 (0)	95.1 (0)

Statistical Analysis 1 for Percentage of Participants Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of subjects with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of subjects with maintained vision for each of the groups treated with VEGF-Trap Eye.
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.4 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus VEGF Trap-Eye. A negative value favors the VEGF Trap-Eye 2.0Q4 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 2 for Percentage of Participants Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 0.5mg Q4
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of subjects with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of subjects with maintained vision for each of the groups treated with VEGF-Trap Eye.
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-1.5
	Confidence Interval	(2-sided) 95.1% -5.1 to 2.1
	Estimation Comments	The difference is calculated as ranibizumab minus VEGF Trap-Eye. A negative value favors the VEGF Trap-Eye 0.5Q4 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

Statistical Analysis 3 for Percentage of Participants Who Maintained Vision at Week 52 - Last Observation Carried Forward (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q8
	Comments	The statistical approach included a conditional sequence of calculations of the 95.1% CI using normal approximation of the difference between the proportion of subjects with maintained vision at Week 52 for the group treated with 0.5 mg ranibizumab and the proportion of subjects with maintained vision for each of the groups treated with VEGF-Trap Eye.
	Type of Statistical Test	Non-Inferiority or Equivalence
	Comments	The non-inferiority margin was set at 10%. The power is 90% according to the sample size estimation of the study protocol. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% non-inferiority margin would be used to assess non-inferiority, a 5% non-inferiority margin would be used to assess clinical equivalence.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.7
	Confidence Interval	(2-sided) 95.1% -4.5 to 3.1
	Estimation Comments	The difference is calculated as ranibizumab minus VEGF Trap-Eye. A negative value favors the VEGF Trap-Eye 2.0Q8 group. As adjustment of multiple comparisons as conditional sequence of statistical hypotheses is used with alpha = 0.049.

2. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.

Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	8.1 (15.25)	10.9 (13.77)	6.9 (13.41)	7.9 (15.00)	8.5 (14.44)

Statistical Analysis 1 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0054
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	3.15
	Confidence Interval	(2-sided) 95.1% 0.92 to 5.37
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4793
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.80
	Confidence Interval	(2-sided) 95.1% -3.03 to 1.43
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8179
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares Means
	Estimated Value	0.26
	Confidence Interval	(2-sided) 95.1% -1.97 to 2.49
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q8.

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.

Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF. Measure Type: Number Unit of Measure: percentage of participants	30.9 (0)	37.5 (0)	24.9 (0)	30.6 (0)	31.1 (0)

Statistical Analysis 1 for Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1042
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	6.6
	Confidence Interval	(2-sided) 95.1% -1.0 to 14.1
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q4.

Statistical Analysis 2 for Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 0.5mg Q4
	Comments	The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1037
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-6.0
	Confidence Interval	(2-sided) 95.1% -13.2 to 1.2
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 0.5Q4.

Statistical Analysis 3 for Percentage of Participants Who Gained at Least 15 Letters of Vision in the ETDRS Letter Score in the Study Eye at Week 52 - LOCF.

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q8
	Comments	The pairwise The null hypothesis is that both percentages are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.93
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	-0.4
	Confidence Interval	(2-sided) 95.1% -7.7 to 7.0
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q8.

4. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF
Measure Description	The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.
Time Frame	Baseline and at Week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.
Total	

Measured Values

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF Measure Type: Mean (Standard Deviation) Unit of Measure: scores on a scale	4.9 (14.01)	6.7 (13.50)	4.5 (11.87)	5.1 (14.74)	5.3 (13.59)

Statistical Analysis 1 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2090
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences Least Squares means
	Estimated Value	1.28
	Confidence Interval	(2-sided) 95.1% -0.73 to 3.28
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q4.

Statistical Analysis 2 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5128
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.67
	Confidence Interval	(2-sided) 95.1% -2.69 to 1.35
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 0.5Q4.

Statistical Analysis 3 for Mean Change From Baseline in National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) Total Score at Week 52 - LOCF

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5579
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.60
	Confidence Interval	(2-sided) 95.1% -2.61 to 1.42
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A positive value favors VEGF Trap-Eye 2.0Q8.

5. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)
Measure Description	CNV area values measured in square millimeters (mm^2); lower values represent better outcomes.
Time Frame	Baseline and at week 52

Analysis Population Description

FAS population used for analysis.

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via IVT injection every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

Total	

Measured Values

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8	Total
Overall Number of Participants Analyzed	304	304	301	301	1210
Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF) Measure Type: Mean (Standard Deviation) Unit of Measure: mm^2	-4.2 (5.59)	-4.6 (5.47)	-3.5 (5.27)	-3.4 (6.02)	-3.9 (5.61)

Statistical Analysis 1 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3575
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	-0.33
	Confidence Interval	(2-sided) 95.1% -1.04 to 0.38
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A negative value favors VEGF Trap-Eye 2.0Q4

Statistical Analysis 2 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 0.5mg Q4
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0507
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.71
	Confidence Interval	(2-sided) 95.1% -0.01 to 1.42
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A negative value favors VEGF Trap-Eye 0.5Q4

Statistical Analysis 3 for Mean Change From Baseline in Choroidal Neovascularization (CNV) Area at Week 52 (LOCF)

Statistical Analysis Overview	Comparison Groups	Ranibizumab 0.5mg Q4, Aflibercept Injection 2.0mg Q8
	Comments	The pairwise comparison is performed as contrast statement in the analysis of covariance model with treatment group as fixed factor (all 4 treatment groups) and the baseline measure as covariate. The null hypothesis is that both mean changes are equal.
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0173
	Comments	As adjustment of multiple comparisons, a conditional sequence of statistical hypotheses is used with alpha = 0.049
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Differences in Least Squares means
	Estimated Value	0.86
	Confidence Interval	(2-sided) 95.1% 0.15 to 1.58
	Estimation Comments	The difference is calculated as VEGF Trap-Eye minus ranibizumab. A negative value favors VEGF Trap-Eye 2.0Q8

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Ranibizumab 0.5mg Q4	Participants received a 0.5mg dose of ranibizumab via intravitreal (IVT) injection every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q4	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 0.5mg Q4	Participants received a 0.5mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 4 weeks for the first year.
Aflibercept Injection 2.0mg Q8	Participants received a 2.0mg dose of aflibercept injection (VEGF Trap-Eye, BAY86-5321) every 8 weeks (including one additional 2.0 mg dose at Week 4) for the first year and were to receive sham injections at interim monthly visits.

All-Cause Mortality

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	/	/	/	/

Serious Adverse Events

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	68/304 (22.37%)	46/304 (15.13%)	56/304 (18.42%)	56/303 (18.48%)
Blood and lymphatic system disorders				
ANAEMIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Cardiac disorders				
ACUTE CORONARY SYNDROME [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ACUTE MYOCARDIAL INFARCTION [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
ANGINA UNSTABLE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
AORTIC VALVE STENOSIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ARRHYTHMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
ATRIAL FIBRILLATION [A*]	2/304 (0.66%)	2/304 (0.66%)	3/304 (0.99%)	3/303 (0.99%)
BRADYCARDIA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CARDIAC ARREST [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CARDIAC FAILURE CHRONIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CARDIAC FAILURE CONGESTIVE [A*]	2/304 (0.66%)	1/304 (0.33%)	2/304 (0.66%)	3/303 (0.99%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
CORONARY ARTERY DISEASE [A*]	4/304 (1.32%)	0/304 (0%)	4/304 (1.32%)	0/303 (0%)
CORONARY ARTERY OCCLUSION [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
INTRACARDIAC THROMBUS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MITRAL VALVE INCOMPETENCE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
MYOCARDIAL INFARCTION [A*]	3/304 (0.99%)	1/304 (0.33%)	3/304 (0.99%)	2/303 (0.66%)
SICK SINUS SYNDROME [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUPRAVENTRICULAR TACHYCARDIA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
TACHYCARDIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
VENTRICULAR FIBRILLATION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VENTRICULAR TACHYCARDIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Congenital, familial and genetic disorders				
ARTERIOVENOUS MALFORMATION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Ear and labyrinth disorders				
MENIERE'S DISEASE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VERTIGO [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
Eye disorders				
ANGLE CLOSURE GLAUCOMA [A] [1]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CATARACT [A] [1]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
KERATITIS A [1]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
MACULAR HOLE A [1]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
POSTERIOR CAPSULE OPACIFICATION A [2]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RETINAL DEGENERATION A [1]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RETINAL DETACHMENT A [2]*	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
RETINAL DETACHMENT A [1]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
RETINAL HAEMORRHAGE A [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL HAEMORRHAGE A [1]*	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
RETINAL OEDEMA A [1]*	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
RETINAL PIGMENT EPITHELIAL TEAR A [1]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL TEAR A [2]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RETINAL TEAR A [1]*	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VISUAL ACUITY REDUCED A [2]*	2/304 (0.66%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
VISUAL ACUITY REDUCED A [1]*	2/304 (0.66%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
Gastrointestinal disorders				
COLITIS ISCHAEMIC A*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
COLONIC POLYP A*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CONSTIPATION A*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DIARRHOEA A*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DUODENAL ULCER HAEMORRHAGE A*	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
GASTRIC ULCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
GASTRITIS EROSIVE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
GASTROINTESTINAL MOTILITY DISORDER [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROOESOPHAGEAL REFLUX DISEASE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMATOCHEZIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HAEMORRHOIDS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
HIATUS HERNIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ILEUS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
INTESTINAL OBSTRUCTION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LOWER GASTROINTESTINAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
General disorders				
ASTHENIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CATHETER SITE HAEMATOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CHEST PAIN [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
DRUG WITHDRAWAL SYNDROME [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
NON-CARDIAC CHEST PAIN [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PYREXIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Hepatobiliary disorders				

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
BILE DUCT STONE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHOLECYSTITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CHOLECYSTITIS CHRONIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHOLELITHIASIS [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PORTAL VEIN THROMBOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Infections and infestations				
ARTHRITIS BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
BRONCHITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
CELLULITIS [A*]	2/304 (0.66%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
CLOSTRIDIAL INFECTION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CLOSTRIDIUM DIFFICILE COLITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DEVICE RELATED INFECTION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
DIVERTICULITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ENDOCARDITIS [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ENDOPHTHALMITIS [A [2]*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
ENDOPHTHALMITIS [A [1]*]	3/304 (0.99%)	3/304 (0.99%)	0/304 (0%)	0/303 (0%)
ESCHERICHIA URINARY TRACT INFECTION [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
GASTROENTERITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	2/303 (0.66%)
LOBAR PNEUMONIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LUNG INFECTION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
PHARYNGITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PNEUMONIA [A*]	7/304 (2.3%)	3/304 (0.99%)	2/304 (0.66%)	5/303 (1.65%)
PYELONEPHRITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SCROTAL ABSCESS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SEPTIC SHOCK [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SINUSITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SINUSITIS FUNGAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
STAPHYLOCOCCAL BACTERAEMIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
URINARY TRACT INFECTION [A*]	1/304 (0.33%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
URINARY TRACT INFECTION BACTERIAL [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VESTIBULAR NEURONITIS [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL INFECTION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
VIRAL PERICARDITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Injury, poisoning and procedural complications				
FALL [A*]	5/304 (1.64%)	6/304 (1.97%)	4/304 (1.32%)	6/303 (1.98%)
FEMUR FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HIP FRACTURE [A*]	1/304 (0.33%)	2/304 (0.66%)	2/304 (0.66%)	0/303 (0%)
HUMERUS FRACTURE [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
INCISIONAL HERNIA, OBSTRUCTIVE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
INCORRECT DOSE ADMINISTERED [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LUMBAR VERTEBRAL FRACTURE [A]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PUBIS FRACTURE [A]*	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RIB FRACTURE [A]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
SNAKE BITE [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SPINAL FRACTURE [A]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SUBCUTANEOUS HAEMATOMA [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SUBDURAL HAEMATOMA [A]*	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	2/303 (0.66%)
TRAUMATIC BRAIN INJURY [A]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
UPPER LIMB FRACTURE [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Investigations				
BLOOD GLUCOSE INCREASED [A]*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
BLOOD PRESSURE INCREASED [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INTRAOCULAR PRESSURE INCREASED [A] [1]*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Metabolism and nutrition disorders				
DEHYDRATION [A]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
DIABETES MELLITUS [A]*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
DIABETES MELLITUS INADEQUATE CONTROL [A]*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
HYPERKALAEMIA [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
HYPOKALAEMIA [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HYPONATRAEMIA [A*]	1/304 (0.33%)	1/304 (0.33%)	1/304 (0.33%)	1/303 (0.33%)
MALNUTRITION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HYPOGLYCAEMIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Musculoskeletal and connective tissue disorders				
BACK PAIN [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INTERVERTEBRAL DISC DEGENERATION [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
INTERVERTEBRAL DISC PROTRUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUMBAR SPINAL STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
OSTEOARTHRITIS [A*]	3/304 (0.99%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPINAL COLUMN STENOSIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPINAL OSTEOARTHRITIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
SPONDYLOLISTHESIS [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
ATYPICAL FIBROXANTHOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
BLADDER TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	1/304 (0.33%)	0/303 (0%)
BREAST CANCER [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
BREAST CANCER IN SITU [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
BRONCHIOLOALVEOLAR CARCINOMA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CHRONIC LYMPHOCYTIC LEUKAEMIA [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
COLON CANCER [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
HEPATIC NEOPLASM MALIGNANT [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
LEUKAEMIA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
LUNG NEOPLASM [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
LUNG NEOPLASM MALIGNANT [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
MALIGNANT MELANOMA [A*]	1/304 (0.33%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
NON-SMALL CELL LUNG CANCER STAGE IV [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
OESOPHAGEAL ADENOCARCINOMA [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PROSTATE CANCER [A*]	1/304 (0.33%)	0/304 (0%)	2/304 (0.66%)	0/303 (0%)
PROSTATE CANCER METASTATIC [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
RECTOSIGMOID CANCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
RENAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
SALIVARY GLAND CANCER RECURRENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SQUAMOUS CELL CARCINOMA OF SKIN [A*]	3/304 (0.99%)	2/304 (0.66%)	1/304 (0.33%)	3/303 (0.99%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
THYROID CANCER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TONSIL CANCER [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
TRANSITIONAL CELL CARCINOMA [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
TUMOUR PERFORATION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
Nervous system disorders				
BALANCE DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
CAROTID ARTERY STENOSIS [A*]	0/304 (0%)	2/304 (0.66%)	0/304 (0%)	0/303 (0%)
CEREBRAL ARTERY THROMBOSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
CEREBRAL HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBRAL INFARCTION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
CEREBROVASCULAR ACCIDENT [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	3/303 (0.99%)
ISCHAEMIC CEREBRAL INFARCTION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
METABOLIC ENCEPHALOPATHY [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SPINAL CORD COMPRESSION [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
SUBARACHNOID HAEMORRHAGE [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
SYNCOPE [A*]	1/304 (0.33%)	1/304 (0.33%)	2/304 (0.66%)	0/303 (0%)
TRANSIENT ISCHAEMIC ATTACK [A*]	0/304 (0%)	2/304 (0.66%)	5/304 (1.64%)	1/303 (0.33%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
Psychiatric disorders				
CONFUSIONAL STATE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
MENTAL STATUS CHANGES [A*]	2/304 (0.66%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PSYCHOTIC DISORDER [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Renal and urinary disorders				
CALCULUS URETERIC [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
RENAL FAILURE ACUTE [A*]	0/304 (0%)	0/304 (0%)	2/304 (0.66%)	1/303 (0.33%)
Reproductive system and breast disorders				
CYSTOCELE [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
Respiratory, thoracic and mediastinal disorders				
APNOEIC ATTACK [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE [A*]	2/304 (0.66%)	3/304 (0.99%)	2/304 (0.66%)	2/303 (0.66%)
PLEURAL EFFUSION [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
PNEUMONIA ASPIRATION [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
PNEUMONITIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	1/303 (0.33%)
PULMONARY EMBOLISM [A*]	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
PULMONARY FIBROSIS [A*]	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
RESPIRATORY FAILURE [A*]	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
Vascular disorders				
AORTIC ANEURYSM [A*]	1/304 (0.33%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
AORTIC ANEURYSM RUPTURE [A*]	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
AORTIC STENOSIS A*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
ARTERIOSCLEROSIS A*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)
DEEP VEIN THROMBOSIS A*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	1/303 (0.33%)
HYPERTENSION A*	2/304 (0.66%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ILIAC ARTERY OCCLUSION A*	0/304 (0%)	0/304 (0%)	1/304 (0.33%)	0/303 (0%)
ORTHOSTATIC HYPOTENSION A*	1/304 (0.33%)	0/304 (0%)	0/304 (0%)	0/303 (0%)
PERIPHERAL ARTERY ANEURYSM A*	0/304 (0%)	1/304 (0.33%)	0/304 (0%)	0/303 (0%)
SHOCK HAEMORRHAGIC A*	0/304 (0%)	0/304 (0%)	0/304 (0%)	1/303 (0.33%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 13.0

[1] Study Eye

[2] Fellow Eye

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	284/304 (93.42%)	280/304 (92.11%)	278/304 (91.45%)	288/303 (95.05%)
Eye disorders				
BLEPHARITIS A [1]*	12/304 (3.95%)	16/304 (5.26%)	10/304 (3.29%)	11/303 (3.63%)
CONJUNCTIVAL HAEMORRHAGE A [2]*	144/304 (47.37%)	109/304 (35.86%)	120/304 (39.47%)	131/303 (43.23%)
EYE IRRITATION A [2]*	16/304 (5.26%)	13/304 (4.28%)	13/304 (4.28%)	12/303 (3.96%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
EYE PAIN [A] [2]*	26/304 (8.55%)	33/304 (10.86%)	27/304 (8.88%)	22/303 (7.26%)
FOREIGN BODY SENSATION IN EYES [A] [2]*	9/304 (2.96%)	8/304 (2.63%)	9/304 (2.96%)	16/303 (5.28%)
MACULAR DEGENERATION [A] [1]*	30/304 (9.87%)	19/304 (6.25%)	25/304 (8.22%)	20/303 (6.6%)
MACULAR DEGENERATION [A] [2]*	16/304 (5.26%)	16/304 (5.26%)	17/304 (5.59%)	10/303 (3.3%)
MACULOPATHY [A] [2]*	19/304 (6.25%)	10/304 (3.29%)	20/304 (6.58%)	8/303 (2.64%)
RETINAL HAEMORRHAGE [A] [1]*	28/304 (9.21%)	20/304 (6.58%)	21/304 (6.91%)	14/303 (4.62%)
RETINAL HAEMORRHAGE [A] [2]*	18/304 (5.92%)	9/304 (2.96%)	17/304 (5.59%)	21/303 (6.93%)
RETINAL PIGMENT EPITHELIOPATHY [A] [2]*	11/304 (3.62%)	16/304 (5.26%)	15/304 (4.93%)	13/303 (4.29%)
VISUAL ACUITY REDUCED [A] [2]*	18/304 (5.92%)	23/304 (7.57%)	21/304 (6.91%)	20/303 (6.6%)
VITREOUS DETACHMENT [A] [1]*	12/304 (3.95%)	16/304 (5.26%)	19/304 (6.25%)	16/303 (5.28%)
VITREOUS DETACHMENT [A] [2]*	24/304 (7.89%)	26/304 (8.55%)	23/304 (7.57%)	19/303 (6.27%)
VITREOUS FLOATERS [A] [2]*	33/304 (10.86%)	40/304 (13.16%)	23/304 (7.57%)	21/303 (6.93%)
Infections and infestations				
BRONCHITIS [A]*	16/304 (5.26%)	12/304 (3.95%)	10/304 (3.29%)	16/303 (5.28%)
NASOPHARYNGITIS [A]*	23/304 (7.57%)	33/304 (10.86%)	24/304 (7.89%)	26/303 (8.58%)
UPPER RESPIRATORY TRACT INFECTION [A]*	13/304 (4.28%)	11/304 (3.62%)	14/304 (4.61%)	18/303 (5.94%)
URINARY TRACT INFECTION [A]*	16/304 (5.26%)	12/304 (3.95%)	15/304 (4.93%)	13/303 (4.29%)
Investigations				
INTRAOCULAR PRESSURE INCREASED [A] [2]*	21/304 (6.91%)	14/304 (4.61%)	12/304 (3.95%)	15/303 (4.95%)

	Ranibizumab 0.5mg Q4	Aflibercept Injection 2.0mg Q4	Aflibercept Injection 0.5mg Q4	Aflibercept Injection 2.0mg Q8
Nervous system disorders				
HEADACHE A*	19/304 (6.25%)	11/304 (3.62%)	11/304 (3.62%)	12/303 (3.96%)
Vascular disorders				
HYPERTENSION A*	23/304 (7.57%)	21/304 (6.91%)	20/304 (6.58%)	20/303 (6.6%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 13.0

[1] Fellow Eye

[2] Study Eye

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Clinical Trials Administrator
Organization: Regeneron Pharmaceuticals
Phone:
Email: clinicaltrials@regeneron.com

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1877 of 2000

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	◉	◉	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: November 1, 2011 (v8)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	November 2011
Overall Status:	Completed
Study Start:	August 2007
Primary Completion:	October 2011 [Actual]
Study Completion:	October 2011 [Actual]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	November 1, 2011
Last Update Posted:	November 6, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor

Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.
Detailed Description:	Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions:	Macular Degeneration
Keywords:	VEGF Trap-Eye Macular Degeneration AMD Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Single Group Assignment
Number of Arms:	
Masking:	Single (Participant)
Allocation:	Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Clinical Trial Management
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	◉	◉	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: June 20, 2011 (v7)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	June 2011
Overall Status:	Active, not recruiting
Study Start:	August 2007
Primary Completion:	October 2011 [Anticipated]
Study Completion:	October 2011 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	June 20, 2011
Last Update Posted:	June 28, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	

Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.
Detailed Description:	Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions:	Macular Degeneration
Keywords:	VEGF Trap-Eye Macular Degeneration AMD Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Single Group Assignment
Number of Arms:	
Masking:	Single (Participant)
Allocation:	Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Kristine Erickson
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	◉	◉	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: April 25, 2011 (v6)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	April 2011
Overall Status:	Active, not recruiting
Study Start:	August 2007
Primary Completion:	October 2011 [Anticipated]
Study Completion:	October 2011 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	April 25, 2011
Last Update Posted:	April 29, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	

Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.
Detailed Description:	Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions:	Macular Degeneration
Keywords:	VEGF Trap-Eye Macular Degeneration AMD Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Single Group Assignment
Number of Arms:	
Masking:	Single (Participant)
Allocation:	Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	◉	◉	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: February 11, 2011 (v5)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	February 2011
Overall Status:	Active, not recruiting
Study Start:	August 2007
Primary Completion:	October 2011 [Anticipated]
Study Completion:	October 2011 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Last Update Submitted that Met QC Criteria:	February 11, 2011
Last Update Posted:	February 14, 2011 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: Single (Participant)

Allocation: Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	◉	◉	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: December 3, 2009 (v4)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

Eye in Subjects With Neovascular Age-related Macular Degeneration

Secondary IDs:

Study Status

Record Verification: December 2009

Overall Status: Active, not recruiting

Study Start: August 2007

Primary Completion: August 2010 [Anticipated]

Study Completion: September 2010 [Anticipated]

First Submitted: September 6, 2007

First Submitted that Met QC Criteria: September 7, 2007

First Posted: September 10, 2007 [Estimate]

Last Update Submitted that Met QC Criteria: December 3, 2009

Last Update Posted: December 4, 2009 [Estimate]

Sponsor/Collaborators

Sponsor: Regeneron Pharmaceuticals

Responsible Party:

Collaborators:

Oversight

U.S. FDA-regulated Drug:

U.S. FDA-regulated Device:

Data Monitoring: No

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: Single (Participant)

Allocation: Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	◉	◉	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: April 9, 2009 (v3)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	April 2009
Overall Status:	Active, not recruiting
Study Start:	August 2007
Primary Completion:	August 2010 [Anticipated]
Study Completion:	September 2010 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Last Update Submitted that Met QC Criteria:	April 9, 2009
Last Update Posted:	April 10, 2009 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: Single (Participant)

Allocation: Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Robert Vitti, MD
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	◉	◉	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: July 3, 2008 (v2)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration

Official Title:	An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	July 2008
Overall Status:	Active, not recruiting
Study Start:	August 2007
Primary Completion:	August 2010 [Anticipated]
Study Completion:	September 2010 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Last Update Submitted that Met QC Criteria:	July 3, 2008
Last Update Posted:	July 8, 2008 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: Single (Participant)

Allocation: Randomized

Enrollment: 165 [Anticipated]

Arms and Interventions

Intervention Details:

Biological: VEGF Trap Eye
Intravitreal injection

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Fort Meyers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33334

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Chicago, Illinois, United States, 60637

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Open-Label, Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	◉	◉	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: September 7, 2007 (v1)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Open-Label, Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration

Official Title:	An Open-Label, Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects With Neovascular Age-Related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	September 2007
Overall Status:	Not yet recruiting
Study Start:	August 2007
Primary Completion:	
Study Completion:	September 2010 [Anticipated]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Last Update Submitted that Met QC Criteria:	September 7, 2007
Last Update Posted:	September 10, 2007 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Open Label Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment. Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms:

Masking: None (Open Label)

Allocation: N/A

Enrollment: 215 [Anticipated]

Arms and Interventions

Intervention Details:

Biological: VEGF Trap Eye
Intravitreal injection

Outcome Measures

Primary Outcome Measures:

1. Safety - Assessment of adverse events and intraocular pressure. Efficacy - Frequency of retreatment between baseline and end of study.
   3 years

Secondary Outcome Measures:

2. Change in letters read from both baseline of this study and baseline of the previous study the subject participated in.
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in:

VGFT-OD-0502 Open-label extension and completed Termination Visit VGFT-OD-0508 Completed through Visit 16 (Week 52) VGFT-OD-0603 Completed through Visit 26 (Week 52)

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Central Contact: Avner Ingerman, MD
Telephone: 914-345-7520
Email: avner.ingerman@regeneron.com

Central Contact Backup: Karen Chu, MS

Telephone: 914-345-7918
Email: karen.chu@regeneron.com

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Fort Meyers, Florida, United States, 33907

Ft. Lauderdale, Florida, United States, 33334

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Chicago, Illinois, United States, 60637

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Kansas

Wichita, Kansas, United States, 67214

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	◉	◉	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: June 10, 2013 (v11)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: A Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	June 2013
Overall Status:	Completed
Study Start:	August 2007
Primary Completion:	October 2011 [Actual]
Study Completion:	October 2011 [Actual]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Results First Submitted:	November 2, 2012
Results First Submitted that Met QC Criteria:	June 10, 2013
Results First Posted:	June 12, 2013 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	June 10, 2013

Last Update Posted: June 12, 2013 [Estimate]

Sponsor/Collaborators

Sponsor: Regeneron Pharmaceuticals

Responsible Party: Sponsor

Collaborators: Bayer

Oversight

U.S. FDA-regulated Drug:

U.S. FDA-regulated Device:

Data Monitoring: No

Study Description

Brief Summary: Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.

Detailed Description: Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions: Macular Degeneration

Keywords: VEGF Trap-Eye
Macular Degeneration
AMD
Neovascular Age-Related Macular Degeneration

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Single Group Assignment

Number of Arms: 1

Masking: Single (Participant)

Allocation: N/A

Enrollment: 157 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye)	Drug: VEGF Trap Eye Intravitreal injection Other Names: • IVT

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation

- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Clinical Trial Management
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	This study was conducted at 35 sites in the United States that participated in the Phase 1 and Phase 2 studies VGFT OD-0502 (NCT00320775), -0508 (NCT00320788), or -0603 (NCT00383370). The recruitment period occurred between 19 Oct 2007 and 29 Oct 2008.
Pre-assignment Details	One hundred fifty seven participants were eligible if they had neovascular Age-related Macular Degeneration (AMD) and completed dosing in the Phase 1 and Phase 2 studies VGFT-OD-0502 (NCT00320775), -0508 (NCT00320788), or -0603 (NCT00383370). For each subject, only one eye was designated as the study eye.

Reporting Groups

	Description
Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152, and a 4-week follow-up visit at week 156. Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or "as needed" dosing). If, at any point during the study, in the investigator's opinion, a participant required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency of injection into the study eye was every 4 weeks.

Overall Study

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Started	157
Completed	120
Not Completed	37
Protocol Violation	1
Adverse Event	5
Physician Decision	4
Withdrawal by Subject	10
Lost to Follow-up	4
OTHER	4
Death	9

Baseline Characteristics

Reporting Groups

	Description

Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152, and a 4-week follow-up visit at week 156. Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or "as needed" dosing). If, at any point during the study, in the investigator's opinion, a participant required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency of injection into the study eye was every 4 weeks.

Baseline Measures

		Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Overall Number of Participants		157
Age Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	157 Participants
		77.9 (8.16)
Sex: Female, Male Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	157 Participants
	Female	96 61.15%
	Male	61 38.85%
Ethnicity (NIH/OMB) Measure type: Count of Participants Unit of measure: Participants	Number Analyzed	157 Participants
	Hispanic or Latino	4 2.55%
	Not Hispanic or Latino	153 97.45%
	Unknown or Not Reported	0 0%
Race (NIH/OMB) Measure type: Count of Participants	Number Analyzed	157 Participants

Unit of measure: Participants		Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
	American Indian or Alaska Native	1 0.64%
	Asian	0 0%
	Native Hawaiian or Other Pacific Islander	0 0%
	Black or African American	0 0%
	White	156 99.36%
	More than one race	0 0%
	Unknown or Not Reported	0 0%
Baseline Best Corrected Visual Acuity (BCVA) [1] Mean (Standard Deviation) Unit of measure: scores on a scale	Number Analyzed	157 Participants
		61.3 (15.35)
		[1] Measure Description: For BCVA, tested via the 4 meter ETDRS (Early Treatment Diabetic Retinopathy Study) protocol, 83 letter or more would represent 20/20 vision or better which would be considered an excellent outcome. Although, the ETDRS charts include 100 letters as the maximum possible score. The worst outcome is 0 letters read.

		Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Baseline Intraocular Pressure [1] Mean (Standard Deviation) Unit of measure: mmHg	Number Analyzed	157 Participants
		14.5 (3.12)
		[1] Measure Description: Intraocular pressure was measured in the study and fellow eyes using applanation tonometry or Tonopen at every study visit pre-dose, and 30 to 60 minutes post-injection.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AE)
Measure Description	Number of participants with AEs summarized by category
Time Frame	Baseline of this study to Wk 152

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152, and a 4-week follow-up visit at week 156. Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or "as needed" dosing). If, at any point during the study, in the investigator's opinion, a participant required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency of injection into the study eye was every 4 weeks.

Measured Values

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Overall Number of Participants Analyzed	157
Number of Participants With Adverse Events (AE) Measure Type: Number Unit of Measure: participants	
Number of participants with any AE	154
Any ocular AE (Study eye and Fellow eye)	138
Any non ocular AE	151
Any treatment related AE (Ocular and non ocular)	5
Any SAE	72
Any AEs leading to withdrawal from study	5
Any Death due to AE	11

2. Secondary Outcome Measure:

Measure Title	Frequency (Number of Injections)
Measure Description	Frequency (number of injections) of PRN treatment from baseline of this study to week 152 (end of treatment).
Time Frame	Baseline of this study to Wk 152

Analysis Population Description

A total of 1116 PRN injections were administered into the study eyes of 135 participants between baseline of this study to Week 152 (end of treatment). Of the 157 enrolled participants, 22 received no injections, and 15 received 1 injection.

Reporting Groups

	Description

Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152 (end of treatment), and a 4-week follow-up visit at week 156 (end of study). Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or

Measured Values

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Overall Number of Participants Analyzed	157
Frequency (Number of Injections) Measure Type: Median (Full Range) Unit of Measure: Injections	6.0 (0 to 26)

3. Secondary Outcome Measure:

Measure Title	Mean Change From Baseline of Original Study in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score of Study Eye - Observed Values
Measure Description	Defined study baseline range of ETDRS Best Corrected Visual Acuity of: letter score of 73 to 25 (20/40 to 20/320) in the study eye; a higher score represents better functioning.
Time Frame	Baseline of original study to Wk 156

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152, and a 4-week follow-up visit at week 156. Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or

Measured Values

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Overall Number of Participants Analyzed	157
Mean Change From Baseline of Original Study in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score of Study Eye - Observed Values Measure Type: Mean (Standard Deviation) Unit of Measure: letters read	4.1 (17.71)

Reported Adverse Events

Time Frame	Baseline of this study to Wk 156
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg	The study consisted of a treatment period from day 1 to week 152, and a 4-week follow-up visit at week 156. Participants were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for an Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) based on his/her assessment of the participant (PRN or "as needed" dosing). If, at any point during the study, in the investigator's opinion, a participant required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency of injection into the study eye was every 4 weeks.

All-Cause Mortality

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
	Affected/At Risk (%)
Total	/

Serious Adverse Events

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
	Affected/At Risk (%)
Total	72/157 (45.86%)
Blood and lymphatic system disorders	
Anaemia [A*]	1/157 (0.64%)
Cardiac disorders	
Acute myocardial infarction [A*]	2/157 (1.27%)
Angina pectoris [A*]	1/157 (0.64%)
Arteriosclerosis coronary artery [A*]	2/157 (1.27%)
Atrial fibrillation [A*]	7/157 (4.46%)
Atrioventricular block [A*]	1/157 (0.64%)
Bradycardia [A*]	2/157 (1.27%)
Cardiac arrest [A*]	1/157 (0.64%)
Cardiac failure congestive [A*]	1/157 (0.64%)
Coronary artery disease [A*]	1/157 (0.64%)
Coronary artery stenosis [A*]	2/157 (1.27%)
Myocardial infarction [A*]	2/157 (1.27%)
Pericarditis [A*]	1/157 (0.64%)
Endocrine disorders	

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Goitre [A*]	1/157 (0.64%)
Eye disorders	
Cataract [A [1]*]	1/157 (0.64%)
Lens dislocation [A [2]*]	1/157 (0.64%)
Retinal haemorrhage [A [1]*]	2/157 (1.27%)
Retinal oedema [A [1]*]	1/157 (0.64%)
Visual acuity reduced [A [1]*]	4/157 (2.55%)
Gastrointestinal disorders	
Diarrhoea [A*]	1/157 (0.64%)
Duodenal ulcer perforation [A*]	1/157 (0.64%)
Eructation [A*]	1/157 (0.64%)
Gastric ulcer [A*]	2/157 (1.27%)
Inguinal hernia [A*]	1/157 (0.64%)
Intestinal obstruction [A*]	1/157 (0.64%)
General disorders	
Chest pain [A*]	1/157 (0.64%)
Gait disturbance [A*]	1/157 (0.64%)
Metaplasia [A*]	1/157 (0.64%)
Hepatobiliary disorders	
Bile duct stone [A*]	1/157 (0.64%)
Cholecystitis [A*]	1/157 (0.64%)
Cholecystitis acute [A*]	1/157 (0.64%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Cholelithiasis [A*]	3/157 (1.91%)
Immune system disorders	
Sarcoidosis [A*]	1/157 (0.64%)
Infections and infestations	
Bronchitis [A*]	2/157 (1.27%)
Cellulitis [A*]	1/157 (0.64%)
Clostridium difficile colitis [A*]	1/157 (0.64%)
Enteritis infectious [A*]	1/157 (0.64%)
Gastroenteritis [A*]	1/157 (0.64%)
Pneumonia [A*]	5/157 (3.18%)
Sepsis [A*]	1/157 (0.64%)
Urinary tract infection [A*]	1/157 (0.64%)
Viral infection [A*]	1/157 (0.64%)
Injury, poisoning and procedural complications	
Accident [A*]	1/157 (0.64%)
Cervical vertebral fracture [A*]	1/157 (0.64%)
Concussion [A*]	1/157 (0.64%)
Corneal abrasion [A [1]*]	1/157 (0.64%)
Facial bones fracture [A*]	1/157 (0.64%)
Fall [A*]	7/157 (4.46%)
Femoral neck fracture [A*]	2/157 (1.27%)
Head injury [A*]	1/157 (0.64%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Incisional hernia [A*]	1/157 (0.64%)
Periorbital haematoma [A*]	1/157 (0.64%)
Pubis fracture [A*]	1/157 (0.64%)
Spinal compression fracture [A*]	1/157 (0.64%)
Investigations	
Intraocular pressure increased [A [2]*]	1/157 (0.64%)
Metabolism and nutrition disorders	
Dehydration [A*]	4/157 (2.55%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A*]	1/157 (0.64%)
Intervertebral disc protrusion [A*]	1/157 (0.64%)
Lumbar spinal stenosis [A*]	1/157 (0.64%)
Osteoarthritis [A*]	4/157 (2.55%)
Rotator cuff syndrome [A*]	1/157 (0.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Adenoma benign [A*]	1/157 (0.64%)
Bladder neoplasm [A*]	1/157 (0.64%)
Bladder transitional cell carcinoma [A*]	1/157 (0.64%)
Breast cancer [A*]	1/157 (0.64%)
Breast cancer metastatic [A*]	1/157 (0.64%)
Breast cancer recurrent [A*]	1/157 (0.64%)
Chronic lymphocytic leukaemia [A*]	1/157 (0.64%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Colon cancer [A*]	2/157 (1.27%)
Head and neck cancer [A*]	2/157 (1.27%)
Lung neoplasm malignant [A*]	1/157 (0.64%)
Lung squamous cell carcinoma stage unspecified [A*]	2/157 (1.27%)
Metastases to liver [A*]	1/157 (0.64%)
Metastatic renal cell carcinoma [A*]	1/157 (0.64%)
Non-small cell lung cancer metastatic [A*]	1/157 (0.64%)
Prostate cancer [A*]	2/157 (1.27%)
Renal cell carcinoma [A*]	1/157 (0.64%)
Renal cell carcinoma recurrent [A*]	1/157 (0.64%)
Small cell lung cancer stage unspecified [A*]	1/157 (0.64%)
Squamous cell carcinoma [A*]	2/157 (1.27%)
Squamous cell carcinoma of skin [A*]	5/157 (3.18%)
Tongue neoplasm malignant stage unspecified [A*]	1/157 (0.64%)
Tonsil cancer [A*]	1/157 (0.64%)
Transitional cell carcinoma [A*]	1/157 (0.64%)
Nervous system disorders	
Basal ganglia haemorrhage [A*]	1/157 (0.64%)
Carotid artery stenosis [A*]	2/157 (1.27%)
Cerebrovascular accident [A*]	2/157 (1.27%)
Dementia [A*]	2/157 (1.27%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Dizziness [A*]	1/157 (0.64%)
Headache [A*]	1/157 (0.64%)
Hypoaesthesia [A*]	1/157 (0.64%)
Lacunar infarction [A*]	1/157 (0.64%)
Presyncope [A*]	1/157 (0.64%)
Syncope [A*]	1/157 (0.64%)
Transient ischaemic attack [A*]	1/157 (0.64%)
Psychiatric disorders	
Hallucination [A*]	1/157 (0.64%)
Mental disorder [A*]	1/157 (0.64%)
Mental status changes [A*]	1/157 (0.64%)
Renal and urinary disorders	
Haematuria [A*]	1/157 (0.64%)
Renal failure [A*]	1/157 (0.64%)
Respiratory, thoracic and mediastinal disorders	
Chronic obstructive pulmonary disease [A*]	1/157 (0.64%)
Dyspnoea [A*]	2/157 (1.27%)
Hypoxia [A*]	1/157 (0.64%)
Pleural effusion [A*]	1/157 (0.64%)
Pulmonary embolism [A*]	2/157 (1.27%)
Pulmonary oedema [A*]	1/157 (0.64%)
Respiratory failure [A*]	1/157 (0.64%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Vascular disorders	
Hypertension [A*]	1/157 (0.64%)
Hypotension [A*]	1/157 (0.64%)
Orthostatic hypotension [A*]	1/157 (0.64%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA Version 14.1

[1] Ocular AE Study Eye

[2] Ocular AE Fellow Eye

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
	Affected/At Risk (%)
Total	149/157 (94.9%)
Blood and lymphatic system disorders	
Anaemia [A*]	8/157 (5.1%)
Eye disorders	
Age-related macular degeneration [A [1]*]	18/157 (11.46%)
Blepharitis [A [1]*]	13/157 (8.28%)
Cataract [A [1]*]	21/157 (13.38%)
Cataract nuclear [A [1]*]	9/157 (5.73%)
Conjunctival haemorrhage [A [1]*]	12/157 (7.64%)
Detachment of retinal pigment epithelium [A [1]*]	8/157 (5.1%)
Dry eye [A [1]*]	10/157 (6.37%)

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Eye pain [A] [1]*	8/157 (5.1%)
Eye pruritus [A] [2]*	8/157 (5.1%)
Posterior capsule opacification [A] [2]*	10/157 (6.37%)
Retinal haemorrhage [A] [1]*	19/157 (12.1%)
Visual acuity reduced [A] [1]*	13/157 (8.28%)
Vitreous detachment [A] [1]*	11/157 (7.01%)
Vitreous floaters [A] [1]*	8/157 (5.1%)
Gastrointestinal disorders	
Constipation [A]*	12/157 (7.64%)
Diarrhoea [A]*	16/157 (10.19%)
Gastrooesophageal reflux disease [A]*	9/157 (5.73%)
Nausea [A]*	14/157 (8.92%)
Immune system disorders	
Seasonal allergy [A]*	15/157 (9.55%)
Infections and infestations	
Bronchitis [A]*	17/157 (10.83%)
Influenza [A]*	10/157 (6.37%)
Nasopharyngitis [A]*	26/157 (16.56%)
Sinusitis [A]*	16/157 (10.19%)
Upper respiratory tract infection [A]*	24/157 (15.29%)
Urinary tract infection [A]*	25/157 (15.92%)
Injury, poisoning and procedural complications	

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Contusion [A*]	10/157 (6.37%)
Fall [A*]	29/157 (18.47%)
Investigations	
Blood glucose increased [A*]	13/157 (8.28%)
Blood pressure increased [A*]	9/157 (5.73%)
Protein urine present [A*]	13/157 (8.28%)
White blood cell count increased [A*]	12/157 (7.64%)
White blood cells urine positive [A*]	9/157 (5.73%)
Metabolism and nutrition disorders	
Hypercholesterolaemia [A*]	9/157 (5.73%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A*]	15/157 (9.55%)
Arthritis [A*]	12/157 (7.64%)
Back pain [A*]	12/157 (7.64%)
Osteoarthritis [A*]	9/157 (5.73%)
Pain in extremity [A*]	9/157 (5.73%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Basal cell carcinoma [A*]	9/157 (5.73%)
Nervous system disorders	
Dizziness [A*]	10/157 (6.37%)
Headache [A*]	8/157 (5.1%)
Psychiatric disorders	

	Intravitreal Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg
Depression [A*]	14/157 (8.92%)
Insomnia [A*]	13/157 (8.28%)
Respiratory, thoracic and mediastinal disorders	
Cough [A*]	14/157 (8.92%)
Dyspnoea [A*]	9/157 (5.73%)
Vascular disorders	
Hypertension [A*]	26/157 (16.56%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA Version 14.1

[1] Ocular AE Fellow Eye

[2] Ocular AE Study Eye

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Clinical Trials Administrator
Organization: Regeneron Pharmaceuticals
Phone:
Email: clinicaltrials@regeneron.com

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	○	○	May 9, 2012	Study Status
10	◉	◉	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: September 27, 2012 (v10)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: A Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	September 2012
Overall Status:	Completed
Study Start:	August 2007
Primary Completion:	October 2011 [Actual]
Study Completion:	October 2011 [Actual]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	September 27, 2012
Last Update Posted:	October 4, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor

Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.
Detailed Description:	Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions:	Macular Degeneration
Keywords:	VEGF Trap-Eye Macular Degeneration AMD Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Single Group Assignment
Number of Arms:	2
Masking:	Single (Participant)
Allocation:	Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Dosing Regimen 1	Drug: VEGF Trap Eye Intravitreal injection Other Names: • IVT
Experimental: Dosing Regimen 2	Drug: VEGF Trap Eye Intravitreal injection Other Names: • IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Clinical Trial Management
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

ClinicalTrials.gov archive

History of Changes for Study: NCT00527423

Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Latest version (submitted June 10, 2013) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	September 7, 2007	None (earliest Version on record)
2	○	○	July 3, 2008	Recruitment Status, Study Status, Study Design, Outcome Measures, Study Identification, Contacts/Locations, Eligibility and Study Description

Version	A	B	Submitted Date	Changes
3	○	○	April 9, 2009	Contacts/Locations, Arms and Interventions, Study Status, Oversight, Sponsor/Collaborators and Study Identification
4	○	○	December 3, 2009	Sponsor/Collaborators and Study Status
5	○	○	February 11, 2011	Study Status and Study Design
6	○	○	April 25, 2011	Study Status
7	○	○	June 20, 2011	Study Status, Contacts/Locations and Sponsor/Collaborators
8	○	○	November 1, 2011	Recruitment Status, Study Status, Sponsor/Collaborators and Contacts/Locations
9	◉	◉	May 9, 2012	Study Status
10	○	○	September 27, 2012	Arms and Interventions, Study Status and Study Identification
11	○	○	June 10, 2013	Outcome Measures, Study Status, More Information, Arms and Interventions, Reported Adverse Events, Baseline Characteristics, Participant Flow and Study Design

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

Scroll up to access the controls

Study NCT00527423

Submitted Date: May 9, 2012 (v9)

Study Identification

Unique Protocol ID: VGFT-OD-0702

Brief Title: Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD

Official Title: An Randomized, Single-Masked , Long-Term, Safety and Tolerability Study of Intravitreal VEGF Trap-

	Eye in Subjects With Neovascular Age-related Macular Degeneration
Secondary IDs:	

Study Status

Record Verification:	November 2011
Overall Status:	Completed
Study Start:	August 2007
Primary Completion:	October 2011 [Actual]
Study Completion:	October 2011 [Actual]
First Submitted:	September 6, 2007
First Submitted that Met QC Criteria:	September 7, 2007
First Posted:	September 10, 2007 [Estimate]
Certification/Extension First Submitted:	April 25, 2011
Certification/Extension First Submitted that Met QC Criteria:	April 25, 2011
Certification/Extension First Posted:	April 29, 2011 [Estimate]
Last Update Submitted that Met QC Criteria:	May 9, 2012
Last Update Posted:	May 14, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Regeneron Pharmaceuticals
Responsible Party:	Sponsor

Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	No

Study Description

Brief Summary:	Rollover study for subjects in prior VEGF Trap-Eye Phase I and II studies. Primary objective is to assess long-term safety and tolerability of continuing intravitreal treatment in subjects with wet age-related macular degeneration.
Detailed Description:	Randomized, Single-Masked Phase II study for subjects previously enrolled in Phase I and II studies for wet age-related macular degeneration with VEGF Trap-Eye intravitreal injection as treatment.Long term (3 years) treatment is intended to measure safety and tolerability, as well as frequency of re-treatment and the effect of VEGF Trap-Eye on best corrected visual acuity (BCVA).

Conditions

Conditions:	Macular Degeneration
Keywords:	VEGF Trap-Eye Macular Degeneration AMD Neovascular Age-Related Macular Degeneration

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Single Group Assignment
Number of Arms:	
Masking:	Single (Participant)
Allocation:	Randomized

Enrollment: 157 [Actual]

Arms and Interventions

Intervention Details:

Drug: VEGF Trap Eye
Intravitreal injection

Other Names:

- IVT

Outcome Measures

Primary Outcome Measures:

1. Assessment of safety and tolerability as assessed by adverse events, laboratory assessments, vital signs, visual acuity and intraocular pressure.
   3 years

Secondary Outcome Measures:

2. The secondary endpoints include: Frequency of re-treatment • Visual acuity parameters (ETDRS letters)
   3 years

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Prior participation in VEGF Trap-Eye Phase I and II studies

Exclusion Criteria:

- Any ocular or systemic adverse events that would preclude participation
- Presence of any condition that would jeopardize subject's participation

Contacts/Locations

Study Officials: Clinical Trial Management
Study Director
Regeneron Pharmaceuticals

Locations: **United States, Arizona**

Peoria, Arizona, United States, 85381

Phoenix, Arizona, United States, 85020

Tucson, Arizona, United States, 85704

United States, California

Beverly Hills, California, United States, 90211

Loma Linda, California, United States, 92354

Palm Springs, California, United States, 92262

Pasadena, California, United States, 91105

Poway, California, United States, 92064

Westlake Village, California, United States, 91361

United States, Florida

Ft. Myers, Florida, United States, 33912

Stuart, Florida, United States, 34994

Winter Haven, Florida, United States, 33880

United States, Georgia

Augusta, Georgia, United States, 30909

United States, Illinois

Glenview, Illinois, United States, 60026

United States, Indiana

Indianapolis, Indiana, United States, 47280

United States, Maryland

Baltimore, Maryland, United States, 21287

Hagerstown, Maryland, United States, 21740

United States, Massachusetts

Boston, Massachusetts, United States, 02114

West Springfield, Massachusetts, United States, 01089

United States, New Jersey

Toms River, New Jersey, United States, 08755

United States, New York

Lynbrook, New York, United States, 11563

United States, North Carolina

Charlotte, North Carolina, United States, 28210

United States, Oklahoma

Oklahoma City, Oklahoma, United States, 73104

United States, Oregon

Portland, Oregon, United States, 97210

United States, South Carolina

W. Columbia, South Carolina, United States, 29169

United States, South Dakota

Rapid City, South Dakota, United States, 57701

United States, Tennessee

Nashville, Tennessee, United States, 37203

United States, Texas

Austin, Texas, United States, 78705

Fort Worth, Texas, United States, 76102

Houston, Texas, United States, 77030

McAllen, Texas, United States, 78503

San Antonio, Texas, United States, 78240

United States, Utah

Salt Lake City, Utah, United States, 84107

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Scroll up to access the controls

Scroll to the Study top

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

U.S. National Library of Medicine

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)

Latest version (submitted November 28, 2014) on ClinicalTrials.gov

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in ~~red~~.
- Study additions are displayed in *green*.

Study Record Versions

Version	A	B	Submitted Date	Changes

Regeneron Ex. 2001
Fresenius v. Regeneron
IPR2025-01269
Page 1984 of 2000

Version	A	B	Submitted Date	Changes
1	○	○	March 17, 2008	None (earliest Version on record)
2	○	○	April 24, 2008	Recruitment Status, Contacts/Locations, Study Status and Oversight
3	○	○	June 19, 2008	Contacts/Locations and Study Status
4	○	○	August 4, 2008	Contacts/Locations, Study Status and Eligibility
5	○	○	September 30, 2008	Contacts/Locations, Study Status, Sponsor/Collaborators, Eligibility and Study Identification
6	○	○	October 2, 2008	Contacts/Locations, Study Status and Study Identification
7	○	○	November 4, 2008	Contacts/Locations, Study Status, Sponsor/Collaborators and Study Identification
8	○	○	December 1, 2008	Study Status and Contacts/Locations
9	○	○	January 5, 2009	Contacts/Locations and Study Status
10	○	○	February 5, 2009	Contacts/Locations and Study Status
11	○	○	March 5, 2009	Contacts/Locations, Study Status, Eligibility and Sponsor/Collaborators
12	○	○	April 2, 2009	Contacts/Locations, Study Status and Eligibility
13	○	○	May 4, 2009	Study Status
14	○	○	June 4, 2009	Contacts/Locations, Study Status and Eligibility
15	○	○	July 3, 2009	Contacts/Locations, Study Status and Eligibility
16	○	○	September 1, 2009	Contacts/Locations, Study Status and Eligibility

Version	A	B	Submitted Date	Changes
17	○	○	September 23, 2009	Recruitment Status, Contacts/Locations and Study Status
18	○	○	November 19, 2009	Study Status
19	○	○	February 19, 2010	Contacts/Locations, Study Status, Arms and Interventions, Study Design and Study Identification
20	○	○	July 9, 2010	Contacts/Locations and Study Status
21	○	○	October 6, 2010	Study Status
22	○	○	November 30, 2010	Contacts/Locations, Study Status and Study Design
23	○	○	February 21, 2011	Study Status
24	○	○	May 23, 2011	Study Status, Contacts/Locations, Sponsor/Collaborators and Study Identification
25	○	○	June 6, 2011	Contacts/Locations, Arms and Interventions, Study Status, Study Identification, Outcome Measures and Sponsor/Collaborators
26	◉	◉	December 16, 2011	Recruitment Status, Study Status, Outcome Measures, Arms and Interventions, Study Identification, Results, References, Contacts/Locations, Eligibility and Study Description
27	○	○	February 27, 2012	Study Status and More Information
28	○	○	March 12, 2013	Reported Adverse Events, Contacts/Locations, Study Status, More Information and References
29	○	○	April 25, 2014	Sponsor/Collaborators, Study Status, More Information, Baseline Characteristics and References
30	○	○	November 28, 2014	Study Status, More Information and References

Compare

Comparison Format: (•) Merged ( ) Side-by-Side

Scroll up to access the controls

Study NCT00637377

Submitted Date: December 16, 2011 (v26)

Study Identification

Unique Protocol ID: 91689

Brief Title: Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)

Official Title: A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)

Secondary IDs: 2007-000583-25 [EudraCT Number]

Study Status

Record Verification: December 2011

Overall Status: Completed

Study Start: April 2008

Primary Completion: September 2010 [Actual]

Study Completion: August 2011 [Actual]

First Submitted: March 12, 2008

First Submitted that Met QC Criteria:	March 17, 2008
First Posted:	March 18, 2008 [Estimate]
Results First Submitted:	December 16, 2011
Results First Submitted that Met QC Criteria:	December 16, 2011
Results First Posted:	January 23, 2012 [Estimate]
Last Update Submitted that Met QC Criteria:	December 16, 2011
Last Update Posted:	January 23, 2012 [Estimate]

Sponsor/Collaborators

Sponsor:	Bayer
Responsible Party:	
Collaborators:	Regeneron Pharmaceuticals

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Data Monitoring:	Yes

Study Description

Brief Summary: This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed Description:	Data of this trial ("VIEW 2") was pooled with data of a sister trial ("VIEW 1", NCT00509795), and an integrated analyses of the combined data was performed.

Conditions

Conditions:	Macular Degeneration
Keywords:	Eye diseases Vision Impairment and Blindness Eyes and Vision Seniors Neovascular Age-Related Macular Degeneration (AMD) Retinal Disease

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	1240 [Actual]

Arms and Interventions

Arms	Assigned Interventions

Arms	Assigned Interventions
Active Comparator: Ranibizumab 0.5mg Q4 Participants received a 0.5 mg dose of Ranibizumab via intravitreal (IVT) injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.	Drug: Ranibizumab Participants received a 0.5 mg dose of Ranibizumab via intravitreal (IVT) injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg Q4 Participants received a 2.0 mg dose of Aflibercept Injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2.0 mg dose of Aflibercept Injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye) 0.5mg Q4 Participants received a 0.5 mg dose of Aflibercept Injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 0.5 mg dose of Aflibercept Injection administered every 4 weeks for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Experimental: Aflibercept Injection (EYLEA, VEGF Trap-Eye) 2mg Q8 Participants received a 2.0 mg dose of Aflibercept Injection administered every 8 weeks (including one additional 2,0 mg dose at Week 4) for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.	Biological: Aflibercept Injection (EYLEA, VEGF Trap-Eye, BAY86-5321) Participants received a 2.0 mg dose of Aflibercept Injection administered every 8 weeks (including one additional 2,0 mg dose at Week 4) for the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 50 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Signed informed consent.
- Men and women >/=50 years of age.
- Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by Fluorescein angiography (FA) in the study eye.
- ETDRS Best-Corrected Visual Acuity letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters.
- Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
- Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria:

- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.

- Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
- Any prior treatment with anti-VEGF agents in the study eye.
- Total lesion size >12 disc areas (30.5 mm, including blood, scars and neovascularization) as assessed by FA in the study eye.
- Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
- Scar or fibrosis making up >50% of the total lesion in the study eye.
- Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
- History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
- Presence of other causes of CNV in the study eye.
- Prior vitrectomy in the study eye.
- History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
- Any history of macular hole of stage 2 and above in the study eye.
- Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
- History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Contacts/Locations

Study Officials: Bayer Study Director
Study Director
Bayer

Locations: **Argentina, Ciudad Auton. de Buenos Aires**

Buenos Aires, Ciudad Auton. de Buenos Aires, Argentina, C1015ABO

Buenos Aires, Ciudad Auton. de Buenos Aires, Argentina, C1023AAQ

Buenos Aires, Ciudad Auton. de Buenos Aires, Argentina, C1122AAI

Buenos Aires, Ciudad Auton. de Buenos Aires, Argentina, C1181ACH

Argentina, Santa Fe

Rosario, Santa Fe, Argentina, S2000ANJ

Argentina

Córdoba, Argentina, X5000IIT

Australia, New South Wales

Chatswood, New South Wales, Australia, 2067

Sydney, New South Wales, Australia, 2000

Westmead, New South Wales, Australia, 2145

Australia, Victoria

East Melbourne, Victoria, Australia, 3002

Parkville, Victoria, Australia, 3050

Australia, Western Australia

Nedlands, Western Australia, Australia, 6009

Australia

Parramatta, Australia, 2150

Austria

Innsbruck, Austria, 6020

Linz, Austria, 4021

Wien, Austria, 1090

Belgium

Liege, Belgium, 4000

Brazil, Sao Paulo

Ribeirão Preto, Sao Paulo, Brazil, 14048-900

São Paulo, Sao Paulo, Brazil, 05651-901

Brazil

Minas Gerais, Brazil, 30150-270

Sao Paulo, Brazil, 04023-062

Colombia, Antioquia

Medellín, Antioquia, Colombia

Colombia, Cauca

Cali, Cauca, Colombia

Colombia, Distrito Capital de Bogotá

Bogota, Distrito Capital de Bogotá, Colombia

Czech Republic

Brno, Czech Republic, 63400

Olonouc, Czech Republic, 77520

Praha 10, Czech Republic, 10034

Praha 4, Czech Republic, 14000

Usti nad Labem, Czech Republic, 401 13

France, Cedex 12

Paris, Cedex 12, France, 75557

France, Cedex 1

Nantes, Cedex 1, France, 44093

France

Besancon, France, 25030

Bordeaux, France, 33000

Dijon, France, 21079

Lyon, France, 69003

Lyon, France, 69006

Marseille, France, 13008

Paris, France, 75010

Paris, France, 75015

Germany, Baden-Württemberg

Freiburg, Baden-Württemberg, Germany, 79106

Heidelberg, Baden-Württemberg, Germany, 69120

Tübingen, Baden-Württemberg, Germany, 72076

Germany, Bayern

München, Bayern, Germany, 81675

Regensburg, Bayern, Germany, 93053

Germany, Hessen

Darmstadt, Hessen, Germany, 64297

Germany, Nordrhein-Westfalen

Aachen, Nordrhein-Westfalen, Germany, 52074

Bonn, Nordrhein-Westfalen, Germany, 53105

Essen, Nordrhein-Westfalen, Germany, 45122

Köln, Nordrhein-Westfalen, Germany, 50924

Münster, Nordrhein-Westfalen, Germany, 48145

Germany, Rheinland-Pfalz

Ludwigshafen, Rheinland-Pfalz, Germany, 67063

Mainz, Rheinland-Pfalz, Germany, 55131

Germany, Saarland

Homburg, Saarland, Germany, 66421

Germany, Sachsen

Dresden, Sachsen, Germany, 01307

Dresden, Sachsen, Germany, 06067

Leipzig, Sachsen, Germany, 04103

Germany, Schleswig-Holstein

Kiel, Schleswig-Holstein, Germany, 24105

Lübeck, Schleswig-Holstein, Germany, 23538

Germany

Berlin, Germany, 12200

Hamburg, Germany, 20251

Hungary

Budapest, Hungary, 1083

Budapest, Hungary, 1106

Budapest, Hungary, 1133

Veszprem, Hungary, 8200

India, Gujrat

Ahemedabad - 4, Gujrat, India, 380009

India, Maharashtra

Wadala, Mumbai, Maharashtra, India, 400031

India, Tamil Nadu

Chennai, Tamil Nadu, India, 600 006

Coimbatore, Tamil Nadu, India, 641014

Madurai, Tamil Nadu, India, 625 020

Pondicherry, Tamil Nadu, India, 600007

India

Bangalore, India, 560010

Chandigarh, India, 160012

Hyderabad, India, 500 034

Kerala, India, 683572

Kolkata, India, 700073

Mumbai, India, 400 050

New Delhi, India, 110002

New Delhi, India, 110029

Orissa, India, 751 024

Israel

Afula, Israel

Beer Sheva, Israel

Haifa, Israel, 34362

Jerusalem, Israel, 91120

Kfar Saba, Israel

Petach Tikva, Israel, 49100

Rehovot, Israel, 76100

Tel Aviv, Israel, 64239

Tel Hashomer, Israel

Zrifin, Israel, 70300

Italy

Ancona, Italy, 60126

Bari, Italy, 70124

Catania, Italy, 95123

Genova, Italy, 16132

Milano, Italy, 20122

Milano, Italy, 20132

Milano, Italy, 20157

Padova, Italy, 35128

Roma, Italy, 00133

Roma, Italy, 00168

Roma, Italy, 00198

Torino, Italy, 10122

Udine, Italy, 33100

Varese, Italy, 21100

Verona, Italy, 37121

Japan, Aichi

Nagoya, Aichi, Japan, 466-8560

Nagoya, Aichi, Japan, 467-8602

Japan, Chiba

Urayasu, Chiba, Japan, 279-0021

Japan, Gunma

Maebashi, Gunma, Japan, 371-8511

Japan, Hokkaido

Sapporo, Hokkaido, Japan, 060-8604

Japan, Kagawa

Kita, Kagawa, Japan, 761-0793

Japan, Osaka

Hirakata, Osaka, Japan, 573-1191

Suita, Osaka, Japan, 565-0871

Japan, Shiga

Otsu, Shiga, Japan, 520-2192

Japan, Tokyo

Chiyoda-ku, Tokyo, Japan, 101-8309

Shinjuku-ku, Tokyo, Japan, 160-8582

Japan

Fukuoka, Japan, 812-8582

Fukushima, Japan, 960-1295

Kagoshima, Japan, 890-8520

Kyoto, Japan, 606-8507

Korea, Republic of, Gyeonggido

Seongnam, Gyeonggido, Korea, Republic of, 463 707

Korea, Republic of

Incheon, Korea, Republic of, 405-760

Seoul, Korea, Republic of, 110 744

Seoul, Korea, Republic of, 137 701

Seoul, Korea, Republic of, 138-736

Seoul, Korea, Republic of, 152-703

Latvia

Riga, Latvia, 1002

Riga, Latvia, 1009

Riga, Latvia, 1050