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(71) Applicant: **Regeneron Pharmaceuticals, Inc.**  
**Tarrytown, NY 10591 (US)**

(72) Inventor: **YANCOPOULOS, George D**  
**Yorktown Heights, NY New York 10598 (US)**

(74) Representative: **J A Kemp**  
**14 South Square**  
**Gray's Inn**  
**London WC1R 5JJ (GB)**

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

(57) The present invention provides methods for  
treating angiogenic eye disorders by sequentially admin-  
istering multiple doses of a VEGF antagonist to a patient.  
The methods of the present invention include the admin-  
istration of multiple doses of a VEGF antagonist to a pa-  
tient at a frequency of once every 8 or more weeks. The

methods of the present invention are useful for the treat-  
ment of angiogenic eye disorders such as age related  
macular degeneration, diabetic retinopathy, diabetic  
macular edema, central retinal vein occlusion and cor-  
neal neovascularization.

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**Description****FIELD OF THE INVENTION**

**[0001]** The present invention relates to the field of therapeutic treatments of eye disorders. More specifically, the invention relates to the administration of VEGF antagonists to treat eye disorders caused by or associated with angiogenesis.

**BACKGROUND**

**[0002]** Several eye disorders are associated with pathological angiogenesis. For example, the development of age-related macular degeneration (AMD) is associated with a process called choroidal neovascularization (CNV). Leakage from the CNV causes macular edema and collection of fluid beneath the macula resulting in vision loss. Diabetic macular edema (DME) is another eye disorder with an angiogenic component. DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy, a disease affecting the blood vessels of the retina. 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. Yet another eye disorder associated with abnormal angiogenesis is 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. The retina can also become ischemic, 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. Thus, inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders.

**[0003]** FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection.

**[0004]** Methods for treating eye disorders using VEGF antagonists are mentioned in, e.g., US 7,303,746; US 7,306,799; US 7,300,563; US 7,303,748; and US 2007/0190058. Nonetheless, there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.

**BRIEF SUMMARY OF THE INVENTION**

**[0005]** The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist to a patient over time. In particular, the methods of the invention comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonists. The present inventors have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present invention, each secondary dose of VEGF antagonist is administered 2 to 4 weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 weeks after the immediately preceding dose. An example of a dosing regimen of the present invention is shown in Figure 1. One advantage of such a dosing regimen is that, for most of the course of treatment (*i.e.*, the tertiary doses), it allows for less frequent dosing (*e.g.*, once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (See, *e.g.*, prescribing information for Lucentis® [ranibizumab], Genentech, Inc.).

**[0006]** The methods of the present invention can be used to treat any angiogenic eye disorder, including, *e.g.*, age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, corneal neovascularization, etc.

**[0007]** The methods of the present invention comprise administering any VEGF antagonist to the patient. In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a "VEGF-Trap" or "VEGFT"). An exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as "VEGFR1R2-FcΔC1(a)" or "aflibercept."

**[0008]** Various administration routes are contemplated for use in the methods of the present invention, including, *e.g.*, topical administration or intraocular administration (*e.g.*, intravitreal administration).

**[0009]** Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients with neovascular (wet) age-related macular degeneration, with a recommended dose of 2 mg

administered by intravitreal injection every 4 weeks for the first three months, followed by 2 mg administered by intravitreal injection once every 8 weeks.

[0010] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

## BRIEF DESCRIPTION OF THE FIGURE

[0011] Figure 1 shows an exemplary dosing regimen of the present invention. In this regimen, a single "initial dose" of VEGF antagonist ("VEGFT") is administered at the beginning of the treatment regimen (*i.e.* at "week 0"), two "secondary doses" are administered at weeks 4 and 8, respectively, and at least six "tertiary doses" are administered once every 8 weeks thereafter, *i.e.*, at weeks 16, 24, 32, 40, 48, 56, etc.).

## DETAILED DESCRIPTION

[0012] Before the present invention is 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.

[0013] 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. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0014] 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.

## DOSING REGIMENS

[0015] The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering to a patient multiple doses of a VEGF antagonist. As used herein, "sequentially administering" means that each dose of VEGF antagonist is administered to the patient at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

[0016] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment.

[0017] In one exemplary embodiment of the present invention, each secondary dose is administered 2 to 4 (*e.g.*, 2, 2½, 3, 3½, or 4) weeks after the immediately preceding dose, and each tertiary dose is administered at least 8 (*e.g.*, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0018] In one exemplary embodiment of the present invention, a single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (*i.e.*, at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (*i.e.*, at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (*i.e.*, at weeks 16, 24, 32, 40 and 48). The tertiary doses may continue (at intervals of 8 or more weeks) indefinitely during the course of the treatment regimen. This exemplary administration regimen is depicted graphically in Figure 1.

[0019] The methods of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of a VEGF antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the

patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0020] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 4 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 8 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. For example, the present invention includes methods which comprise administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by at least 5 tertiary doses of the VEGF antagonist, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered from 8 to 12 (e.g., 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12) weeks after the immediately preceding dose. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

## VEGF ANTAGONISTS

[0021] The methods of the present invention comprise administering to a patient a VEGF antagonist according to specified dosing regimens. As used herein, the expression "VEGF antagonist" means any molecule that blocks, reduces or interferes with the normal biological activity of VEGF.

[0022] VEGF antagonists include molecules which interfere with the interaction between VEGF and a natural VEGF receptor, e.g., molecules which bind to VEGF or a VEGF receptor and prevent or otherwise hinder the interaction between VEGF and a VEGF receptor. Specific exemplary VEGF antagonists include anti-VEGF antibodies, anti-VEGF receptor antibodies, and VEGF receptor-based chimeric molecules (also referred to herein as "VEGF-Traps").

[0023] VEGF receptor-based chimeric molecules include chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (e.g., an Fc domain which facilitates the multimerization [e.g., dimerization] of two or more chimeric polypeptides). An exemplary VEGF receptor-based chimeric molecule is a molecule referred to as VEGFR1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1. VEGFR1R2-FcΔC1(a) comprises three components: (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and (3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acid of SEQ ID NO:2 [i.e., K458] may or may not be included in the VEGF antagonist used in the methods of the invention; see e.g., US Patent 7,396,664). Amino acids 1-26 of SEQ ID NO:2 are the signal sequence.

[0024] The VEGF antagonist used in the Examples set forth herein below is a dimeric molecule comprising two VEGFR1R2-FcΔC1(a) molecules and is referred to herein as "VEGFT." Additional VEGF receptor-based chimeric molecules which can be used in the context of the present invention are disclosed in US 7,396,664, 7,303,746 and WO 00/75319.

## ANGIOGENIC EYE DISORDERS

[0025] The methods of the present invention can be used to treat any angiogenic eye disorder. The expression "angiogenic eye disorder," as used herein, means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include choroidal neovascularization, age-related macular degeneration (AMD), diabetic retinopathies, diabetic macular edema (DME), central retinal vein occlusion (CRVO), corneal neovascularization, and retinal neovascularization.

## PHARMACEUTICAL FORMULATIONS

[0026] The present invention includes methods in which the VEGF antagonist that is administered to the patient is contained within a pharmaceutical formulation. The pharmaceutical formulation may comprise the VEGF antagonist along with at least one inactive ingredient such as, e.g., a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical composition to provide improved transfer, delivery, tolerance, and the like. 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 antibody is administered. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's

Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in the context of the methods of the present invention, provided that the VEGF antagonist is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

**[0027]** Pharmaceutical formulations useful for administration by injection in the context of the present invention may be prepared by dissolving, suspending or emulsifying a VEGF antagonist in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there may be employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule if desired.

## **MODES OF ADMINISTRATION**

**[0028]** The VEGF antagonist (or pharmaceutical formulation comprising the VEGF antagonist) may be administered to the patient by any known delivery system and/or administration method. In certain embodiments, the VEGF antagonist is administered to the patient by ocular, intraocular, intravitreal or subconjunctival injection. In other embodiments, the VEGF antagonist can be administered to the patient by topical administration, e.g., via eye drops or other liquid, gel, ointment or fluid which contains the VEGF antagonist and can be applied directly to the eye. Other possible routes of administration include, e.g., intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral.

## **AMOUNT OF VEGF ANTAGONIST ADMINISTERED**

**[0029]** Each dose of VEGF antagonist administered to the patient over the course of the treatment regimen may contain the same, or substantially the same, amount of VEGF antagonist. Alternatively, the quantity of VEGF antagonist contained within the individual doses may vary over the course of the treatment regimen. For example, in certain embodiments, a first quantity of VEGF antagonist is administered in the initial dose, a second quantity of VEGF antagonist is administered in the secondary doses, and a third quantity of VEGF antagonist is administered in the tertiary doses. The present invention contemplates dosing schemes in which the quantity of VEGF antagonist contained within the individual doses increases over time (e.g., each subsequent dose contains more VEGF antagonist than the last), decreases over time (e.g., each subsequent dose contains less VEGF antagonist than the last), initially increases then decreases, initially decreases then increases, or remains the same throughout the course of the administration regimen.

**[0030]** The amount of VEGF antagonist administered to the patient in each dose is, in most cases, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, lessens, or delays the progression of an angiogenic eye disorder. In the case of an anti-VEGF antibody or a VEGF receptor-based chimeric molecule such as VEGFR1R2-FcΔC1(a), a therapeutically effective amount can be from about 0.05 mg to about 5 mg, e.g., about 0.05 mg, about 0.1 mg, about 0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.85 mg, about 0.9 mg, about 1.0 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 2.0 mg, about 2.05 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, about 2.75 mg, about 2.8 mg, about 2.85 mg, about 2.9 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, or about 5.0 mg of the antibody or receptor-based chimeric molecule.

**[0031]** The amount of VEGF antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (*i.e.*, mg/kg). For example, the VEGF antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

**TREATMENT POPULATION AND EFFICACY**

5 **[0032]** The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder. Generally, the methods of the present invention demonstrate efficacy within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at "week 0"), e.g., by the end of week 16, by the end of week 24, by the end of week 32, by the end of week 40, by the end of week 48, by the end of week 56, etc. In the context of methods for treating angiogenic eye disorders such as AMD, CRVO, and DME, "efficacy" means that, from the initiation of treatment, the patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. In certain  
10 embodiments, "efficacy" means a gain of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) letters on the ETDRS chart from the time of initiation of treatment.

**EXAMPLES**

15 **[0033]** The following examples are 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  
20 degrees Centigrade, and pressure is at or near atmospheric.

**[0034]** The exemplary VEGF antagonist used in all Examples set forth below is a dimeric molecule having two functional VEGF binding units. Each functional binding unit is comprised of Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of a human IgG1 Fc domain (VEGFR1 R2-FcΔC1 (a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the example below as "VEGFT". For purposes of the following  
25 Examples, "monthly" dosing is equivalent to dosing once every four weeks.

**Example 1: Phase I Clinical Trial of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD**

30 **[0035]** In this Phase I study, 21 subjects with neovascular AMD received a single intravitreal (IVT) dose of VEGFT. Five groups of three subjects each received either 0.05, 0.15, 0.5, 2 or 4 mg of VEGFT, and a sixth group of six subjects received 1 mg. No serious adverse events related to the study drug, and no identifiable intraocular inflammation was reported. Preliminary results showed that, following injection of VEGFT, a rapid decrease in foveal thickness and macular volume was observed that was maintained through 6 weeks. At Day 43 across all dose groups, mean excess retinal thickness [excess retinal thickness = (retinal thickness - 179μ)] on optical coherence tomography (OCT) was reduced  
35 from 119μ to 27μ as assessed by Fast Macular Scan and from 194μ to 60μ as assessed using a single Posterior Pole scan. The mean increase in best corrected visual acuity (BCVA) was 4.75 letters, and BCVA was stable or improved in 95% of subjects. In the 2 highest dose groups (2 and 4 mg), the mean increase in BCVA was 13.5 letters, with 3 of 6 subjects demonstrating improvement of ≥ 3 lines.

**Example 2: Phase II Clinical Trial of Repeated Doses of Intravitreally Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD**

45 **[0036]** This study was a double-masked, randomized study of 3 doses (0.5, 2, and 4 mg) of VEGFT tested at 4-week and/or 12-week dosing intervals. There were 5 treatment arms in this study, as follows: 1) 0.5 mg every 4 weeks, 2) 0.5 mg every 12 weeks, 3) 2 mg every 4 weeks, 4) 2 mg every 12 weeks and 5) 4 mg every 12 weeks. Subjects were dosed at a fixed interval for the first 12 weeks, after which they were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria. All subjects were then followed for one year after their last dose of VEGFT. Preliminary data from a pre-planned interim analysis indicated that VEGFT met its primary  
50 endpoint of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline (all groups combined, decrease of 135μ, p < 0.0001). Mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.9 letters, p < 0.0001). Moreover, patients in the dose groups that received only a single dose, on average, demonstrated a decrease in excess retinal thickness (p < 0.0001) and an increase in visual acuity (p = 0.012) at 12 weeks. There were no drug-related  
55 serious adverse events, and treatment with the VEGF antagonists was generally well-tolerated. The most common adverse events were those typically associated with intravitreal injections.

**Example 3: Phase I Clinical Trial of Systemically Administered VEGF Receptor-Based Chimeric Molecule (VEGFT) in Subjects with Neovascular AMD**

**[0037]** This study was a placebo-controlled, sequential-group, dose-escalating safety, tolerability and bioeffect study of VEGFT by IV infusion in subjects with neovascular AMD. Groups of 8 subjects meeting eligibility criteria for subfoveal choroidal neovascularization (CNV) related to AMD were assigned to receive 4 IV injections of VEGFT or placebo at dose levels of 0.3, 1, or 3 mg/kg over an 8-week period.

**[0038]** Most adverse events that were attributed to VEGFT were mild to moderate in severity, but 2 of 5 subjects treated with 3 mg/kg experienced dose-limiting toxicity (DLT) (one with Grade 4 hypertension and one with Grade 2 proteinuria); therefore, all subjects in the 3 mg/kg dose group did not enter the study. The mean percent changes in excess retinal thickness were: ~12%, ~10%, ~66%, and ~60% for the placebo, 0.3, 1, and 3 mg/kg dose groups at day 15 (ANOVA  $p < 0.02$ ), and -5.6%, +47.1%, and ~63.3% for the placebo, 0.3, and 1 mg/kg dose groups at day 71 (ANOVA  $p < 0.02$ ). There was a numerical improvement in BCVA in the subjects treated with VEGFT. As would be expected in such a small study, the results were not statistically significant.

**Example 4: Phase III Clinical Trials of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGFT in Subjects with Neovascular Age-Related Macular Degeneration**

**A. Objectives, Hypotheses and Endpoints**

**[0039]** Two parallel Phase III clinical trials were carried out to investigate the use of VEGFT to treat patients with the neovascular form of age-related macular degeneration (Study 1 and Study 2). The primary objective of these studies was to assess the efficacy of IVT administered VEGFT compared to ranibizumab (Lucentis®, Genentech, Inc.), in a non-inferiority paradigm, in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.

**[0040]** The secondary objectives were (a) to assess the safety and tolerability of repeated IVT administration of VEGFT in subjects with all sub-types of neovascular AMD for periods up to 2 years; and (b) to assess the effect of repeated IVT administration of VEGFT on Vision-Related Quality of Life (QOL) in subjects with all sub-types of neovascular AMD.

**[0041]** The primary hypothesis of these studies was that the proportion of subjects treated with VEGFT with stable or improved BCVA (<15 letters lost) is similar to the proportion treated with ranibizumab who have stable or improved BCVA, thereby demonstrating non-inferiority.

**[0042]** The primary endpoint for these studies was the prevention of vision loss of greater than or equal to 15 letters on the ETDRS chart, compared to baseline, at 52 weeks. Secondary endpoints were as follows: (a) change from baseline to Week 52 in letter score on the ETDRS chart; (b) gain from baseline to Week 52 of 15 letters or more on the ETDRS chart; (c) change from baseline to Week 52 in total NEI VFQ-25 score; and (d) change from baseline to Week 52 in CNV area.

**B. Study Design**

**[0043]** For each study, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: (1) 2 mg VEGFT administered every 4 weeks (2Q4); (2) 0.5 mg VEGFT administered every 4 weeks (0.5Q4); (3) 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks (with sham injection at the interim 4-week visits when study drug was not administered (2Q8)); and (4) 0.5 mg ranibizumab administered every 4 weeks (RQ4). Subjects assigned to (2Q8) received the 2 mg injection every 4 weeks to week 8 and then a sham injection at interim 4-week visits (when study drug is not to be administered) during the first 52 weeks of the studies. (No sham injection were given at Week 52).

**[0044]** The study duration for each subject was scheduled to be 96 weeks plus the recruitment period. For the first 52 weeks (Year 1), subjects received an IVT or sham injection in the study eye every 4 weeks. (No sham injections were given at Week 52). During the second year of the study, subjects will be evaluated every 4 weeks and will receive IVT injection of study drug at intervals determined by specific dosing criteria, but at least every 12 weeks. (During the second year of the study, sham injections will not be given.) During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to the following criteria: (i) increase in central retinal thickness of  $\geq 100 \mu\text{m}$  compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

**[0045]** Subjects were evaluated at 4 weeks intervals for safety and best corrected visual acuity (BCVA) using the 4 meter ETDRS protocol. Quality of Life (QOL) was evaluated using the NEI VFQ-25 questionnaire. OCT and FA examinations were conducted periodically.

**[0046]** Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

**[0047]** To be eligible for this study, subjects were required to have subfoveal choroidal neovascularization (CNV) secondary to AMD. "Subfoveal" CNV was defined as the presence of subfoveal neovascularization, documented by FA, or presence of a lesion that is juxtafoveal in location angiographically but affects the fovea. Subject eligibility was confirmed based on angiographic criteria prior to randomization.

**[0048]** Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and subject preference were considered in making the selection.

**[0049]** Inclusion criteria for both studies were as follows: (i) signed Informed consent; (ii) at least 50 years of age; (iii) active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye; (iv) CNV at least 50% of total lesion size; (v) early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye; (vi) willing, committed, and able to return for all clinic visits and complete all study-related procedures; and (vii) able to read, understand and willing to sign the informed consent form (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member).

**[0050]** Exclusion criteria for both studies were as follows: 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: (a) Prior treatment with anti-VEGF therapy in the study eye was not allowed; (b) Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an approved anti-VEGF therapy in the fellow eye was allowed; (c) Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved, was only allowed up to 3 months prior to first dose, and was not allowed during the study. 4. Total lesion size > 12 disc areas (30.5 mm<sup>2</sup>, 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 it was unlikely to interfere with the injection. 16. Prior trabeculectomy or other filtration surgery in the study eye. 17. Uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication) in the study eye. 18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye. 20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye. 21. Any history of uveitis in either eye. 22. Active scleritis or episcleritis in either eye. 23. Presence or history of scleromalacia in either eye. 24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye. 25. Previous therapeutic radiation in the region of the study eye. 26. History of corneal transplant or corneal dystrophy in the study eye. 27. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography. 28. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period. 29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. 30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. 31. Participation as a subject in any clinical study within the 12 weeks prior to Day 1. 32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1. 33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. 34. Any history of allergy to povidone iodine. 35. Known serious allergy to the fluorescein sodium for injection in angiography. 36. Presence of any contraindications indicated in the FDA

Approved label for ranibizumab (Lucentis®). 37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

**[0051]** Subjects were not allowed to receive any standard or investigational agents for treatment of their AMD in the study eye other than their assigned study treatment with VEGFT or ranibizumab as specified in the protocol until they completed the Completion/Early Termination visit assessments. This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the study and/or fellow eye.

**[0052]** The study procedures are summarized as follows:

Best Corrected Visual Acuity: Visual function of the study eye and the fellow eye were assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group) at 4 meters. Visual Acuity examiners were certified to ensure consistent measurement of BCVA. The VA examiners were required to remain masked to treatment assignment.

Optical Coherence Tomography: Retinal and lesion characteristics were evaluated using OCT on the study eye. At the Screen Visit (Visit 1) images were captured and transmitted for both eyes. All OCT images were captured using the Zeiss Stratus OCT™ with software Version 3 or greater. OCT images were sent to an independent reading center where images were read by masked readers at visits where OCTs were required. All OCTs were electronically archived at the site as part of the source documentation. A subset of OCT images were read. OCT technicians were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that OCT technicians at the site remained masked to treatment assignment.

Fundus Photography and Fluorescein Angiography (FA): The anatomical state of the retinal vasculature of the study eye was evaluated by funduscopic examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopic examination, fundus photography and FA were captured and transmitted for both eyes. Fundus and angiographic images were sent to an independent reading center where images were read by masked readers. The reading center confirmed subject eligibility based on angiographic criteria prior to randomization. All FAs and fundus photographs were archived at the site as part of the source documentation. Photographers were required to be certified by the reading center to ensure consistency and quality in image acquisition. Adequate efforts were made to ensure that all photographers at the site remain masked to treatment assignment.

Vision-Related Quality of Life: Vision-related QOL was assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) in the interviewer-administered format. NEI VFQ-25 was administered by certified personnel at a contracted call center. At the screening visit, the sites assisted the subject and initiated the first call to the call center to collect all of the subject's contact information and to complete the first NEI VFQ-25 on the phone prior to randomization and IVT injection. For all subsequent visits, the call center called the subject on the phone, prior to IVT injection, to complete the questionnaire.

Intraocular Pressure: Intraocular pressure (IOP) of the study eye was measured using applanation tonometry or Tonopen. The same method of IOP measurement was used in each subject throughout the study.

### C. Results Summary (52 Week Data)

**[0053]** The primary endpoint (prevention of moderate or severe vision loss as defined above) was met for all three VEGFT groups (2Q4, 0.5Q4 and 2Q8) in this study. The results from both studies are summarized in Table 1.

**Table 1**

|                                                                                       | Ranibizumab 0.5 mg monthly (RQ4) | VEGFT 0.5 mg monthly (0.5Q4) | VEGFT 2 mg monthly (2Q4) | VEGFT 2 mg every 8 weeks <sup>[a]</sup> (2Q8) |
|---------------------------------------------------------------------------------------|----------------------------------|------------------------------|--------------------------|-----------------------------------------------|
| Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline     |                                  |                              |                          |                                               |
| Study 1                                                                               | 94.4%                            | 95.9%**                      | 95.1%**                  | 95.1%**                                       |
| Study 2                                                                               | 94.4%                            | 96.3%**                      | 95.6%**                  | 95.6%**                                       |
| Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)*** |                                  |                              |                          |                                               |
| Study 1                                                                               | 8.1                              | 6.9 (NS)                     | 10.9(p<0.01)             | 7.9 (NS)                                      |

(continued)

|                                                                                                                                                                                                                                                                                                                                                                                                                                 | Ranibizumab 0.5 mg monthly (RQ4) | VEGFT 0.5 mg monthly (0.5Q4) | VEGFT 2 mg monthly (2Q4) | VEGFT 2 mg every 8 weeks <sup>[a]</sup> (2Q8) |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------------|--------------------------|-----------------------------------------------|
| Study 2                                                                                                                                                                                                                                                                                                                                                                                                                         | 9.4                              | 9.7 (NS)                     | 7.6 (NS)                 | 8.9 (NS)                                      |
| <sup>[a]</sup> Following three initial monthly doses<br>* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.<br>** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)<br>*** Test for superiority<br>NS = non-significant |                                  |                              |                          |                                               |

**[0054]** In Study 1, patients receiving VEGFT 2mg monthly (2Q4) achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly (RQ4); patients receiving VEGFT 2mg monthly on average gained 10.9 letters, compared to a mean 8.1 letter gain with ranibizumab 0.5mg dosed every month ( $p < 0.01$ ). All other dose groups of VEGFT in Study 1 and all dose groups in Study 2 were not statistically different from ranibizumab in this secondary endpoint.

**[0055]** A generally favorable safety profile was observed for both VEGFT 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.

#### Example 5: Phase II Clinical Trial of VEGFT in Subjects with Diabetic Macular Edema (DME)

**[0056]** In this study, 221 patients with clinically significant DME with central macular involvement were randomized, and 219 patients were treated with balanced distribution over five groups. The control group received macular laser therapy at baseline, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. The remaining four groups received VEGFT by intravitreal injection as follows: Two groups received 0.5 or 2 mg of VEGFT once every four weeks throughout the 12-month dosing period (0.5Q4 and 2Q4, respectively). Two groups received three initial doses of 2 mg VEGFT once every four weeks (*i.e.*, at baseline, and weeks 4 and 8), followed through week 52 by either once every 8 weeks dosing (2Q8) or as needed dosing with very strict repeat dosing criteria (PRN). Mean gains in visual acuity versus baseline were as shown in Table 2:

Table 2

|                                                                                    | n  | Mean change in visual acuity, at week 24 versus baseline (letters) | Mean change in visual acuity at week 52 versus baseline (letters) |
|------------------------------------------------------------------------------------|----|--------------------------------------------------------------------|-------------------------------------------------------------------|
| Laser                                                                              | 44 | 2.5                                                                | -1.3                                                              |
| VEGFT 0.5 mg monthly (0.5Q4)                                                       | 44 | 8.6**                                                              | 11.0**                                                            |
| VEGFT 2 mg monthly (2Q4)                                                           | 44 | 11.4**                                                             | 13.1**                                                            |
| VEGFT 2 mg every 8 weeks <sup>[a]</sup> (2Q8)                                      | 42 | 8.5**                                                              | 9.7**                                                             |
| VEGFT 2 mg as needed <sup>[a]</sup> (PRN)                                          | 45 | 10.3**                                                             | 12.0**                                                            |
| <sup>[a]</sup> Following three initial monthly doses<br>** $p < 0.01$ versus laser |    |                                                                    |                                                                   |

[0057] In this study, the visual acuity gains achieved with VEGFT administration at week 24 were maintained or numerically improved up to completion of the study at week 52 in all VEGFT study groups, including 2 mg dosed every other month

[0058] As demonstrated in the foregoing Examples, the administration of VEGFT to patients suffering from angiogenic eye disorders (e.g., AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity.

#### Example 6: A Randomized, Multicenter, Double-Masked Trial in Treatment Naïve Patients with Macular Edema Secondary to CRVO

[0059] In this randomized, double-masked, Phase 3 study, patients received 6 monthly injections of either 2 mg intravitreal VEGFT (114 patients) or sham injections (73 patients). From Week 24 to Week 52, all patients received 2 mg VEGFT as-needed (PRN) according to retreatment criteria. Thus, "sham-treated patients" means patients who received sham injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. "VEGFT-treated patients" means patients who received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed from Week 24 through Week 52. The primary endpoint was the proportion of patients who gained  $\geq 15$  ETDRS letters from baseline at Week 24. Secondary visual, anatomic, and Quality of Life NEI VFQ-25 outcomes at Weeks 24 and 52 were also evaluated.

[0060] At Week 24, 56.1 % of VEGFT-treated patients gained  $\geq 15$  ETDRS letters from baseline vs 12.3% of sham-treated patients ( $P < 0.0001$ ). Similarly, at Week 52, 55.3% of VEGFT-treated patients gained  $\geq 15$  letters vs 30.1% of sham-treated patients ( $P < 0.01$ ). At Week 52, VEGFT-treated patients gained a mean of 16.2 letters vs 3.8 letters for sham-treated patients ( $P < 0.001$ ). Mean number of injections was 2.7 for VEGFT-treated patients vs 3.9 for sham-treated patients. Mean change in central retinal thickness was  $-413.0 \mu\text{m}$  for VEGFT-treated patients vs  $-381.8 \mu\text{m}$  for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

[0061] This Example confirms that dosing monthly with 2 mg intravitreal VEGFT injection resulted in a statistically significant improvement in visual acuity at Week 24 that was maintained through Week 52 with PRN dosing compared with sham PRN treatment. VEGFT was generally well tolerated and had a generally favorable safety profile.

#### SEQUENCES

[0062] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTC  
 ACAGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCC  
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 10 TTCTGACCTGTGAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGA  
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 15 GGGAATACCCTTCTTCGAAGCATCAGCATAAGAACTTGTAACCGAGACCTAAAAACCCA  
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 GACCAAGGATTGTACACCTGTGCAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACA  
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 TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT  
 25 CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG  
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 30 AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC  
 CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT  
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACATAAG  
 35 ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTG  
 GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG  
 CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

40 [0063] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITV  
 45 TLKKFPLDTLIPDGKRIIWDNRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYTHRQNTIIDVVL  
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 IDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTCPPCPAPELLGGPSVFLFPPKPKD  
 50 TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD  
 WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD  
 IAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVSMHEALHNHYTQ  
 55 KSLSLSPGK

[0064] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the

art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

#### **Further Numbered Embodiments of the Invention:**

**[0065]** The following represent further numbered embodiments of the invention, but do not at present represent claims:

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.
2. The method of item 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.
3. The method of item 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.
4. The method of item 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.
5. The method of item 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.
6. The method of item 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.
7. The method of item 6, wherein the angiogenic eye disorder is age related macular degeneration.
8. The method of item 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.
9. The method of item 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.
10. The method of item 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.
11. The method of item 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.
12. The method of item 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.
13. The method of item 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
14. The method of item 13, wherein the intraocular administration is intravitreal administration.
15. The method of item 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.
16. The method of item 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
17. The method of item 16, wherein the intraocular administration is intravitreal administration.

18. The method of item 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.
19. The method of item 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.
20. The method of item 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.
21. A VEGF antagonist for use in a method of treating an angiogenic eye disorder in a patient, wherein the method comprises sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.
22. The VEGF antagonist of item 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.
23. The VEGF antagonist of item 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.
24. The VEGF antagonist of any one of items 21 to 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.
25. The VEGF antagonist of any one of items 21 to 23, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.
26. The VEGF antagonist of any one of items 21 to 25, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.
27. The VEGF antagonist of item 26, wherein the angiogenic eye disorder is age related macular degeneration.
28. The VEGF antagonist of any one of items 21 to 27, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.
29. The VEGF antagonist of item 28, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.
30. The VEGF antagonist of item 29, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.
31. The VEGF antagonist of item 29, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.
32. The VEGF antagonist of any one of items 21 to 31, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.
33. The VEGF antagonist of item 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
34. The VEGF antagonist of item 33, wherein the intraocular administration is intravitreal administration.
35. The VEGF antagonist of item 34, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.
36. The VEGF antagonist of item 35, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

37. The VEGF antagonist of item 35, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

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## SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.

5 <120> Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

<130> 725A-WO

<140> To be assigned

10 <141> Filed herewith

<150> 61/432,245

<151> 2011-01-13

<150> 61/434,836

15 <151> 2011-01-21

<150> 61/561,957

<151> 2011-11-21

20 <160> 2

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25 <211> 1377

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

30 <400> 1

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| cccgaatta   | tacacatgac  | tgaaggaag   | gagctcgtca | ttccctgccg | ggttacgtca  | 180  |
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| cgcataatct  | gggacagtag  | aaagggcttc  | atcatatcaa | atgcaacgta | caaagaaata  | 300  |
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| aagccgcggg  | aggagcagta  | caacagcacg  | taccgtgtgg | tcagcgtcct | caccgtcctg  | 960  |
| caccaggact  | ggctgaatgg  | caaggagtac  | aagtgcagg  | tctccaacaa | agccctccca  | 1020 |
| gcccccatcg  | agaaaacat   | ctccaaagcc  | aaagggcagc | cccgagaacc | acaggtgtac  | 1080 |
| accctgcccc  | catcccggga  | tgagctgacc  | aagaaccagg | tcagcctgac | ctgcctggtc  | 1140 |
| aaaggcttct  | atcccagcga  | catcgccgtg  | gagtgggaga | gcaatgggca | gccgggagaac | 1200 |
| aactacaaga  | ccacgcctcc  | cgtgctggac  | tccgacggct | ccttcttctc | ctacagcaag  | 1260 |
| ctcaccgtgg  | acaagagcag  | gtggcagcag  | gggaacgtct | tctcatgctc | cgtgatgcat  | 1320 |
| gaggctctgc  | acaaccacta  | cacgcagaag  | agcctctccc | tgtctccggg | taaatga     | 1377 |

<210> 2

55 <211> 458

<212> PRT

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthetic

&lt;400&gt; 2

|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5  | 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  |     |     |     |
| 10 | 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 |
| 15 |     |     |     | 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 |     |     |     |
| 20 | 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 |     |     |
| 25 | 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 |     |     |     |     |
| 30 | 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 |
| 35 |     |     |     | 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 |     |     |     |     |
| 40 | 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 |     |     |
| 45 | 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 |     |
| 50 | 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 |     |     |     |
| 55 | Gln | Lys | Ser | Leu | Ser | Leu | Ser | Pro | Gly | Lys |     |     |     |     |     |     |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     |     |     |     |     |     |

## Claims

1. A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose; wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and wherein the VEGF antagonist comprises VEGFR1 R2-Fc $\Delta$ C1 (a) encoded by the nucleic acid sequence of SEQ ID NO:1.
2. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is age related macular degeneration.
3. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic retinopathy.
4. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic macular edema.
5. The VEGF antagonist for according to claim 1, wherein the angiogenic eye disorder is central retinal vein occlusion.
6. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is corneal neovascularization.
7. The VEGF antagonist for use according to any one of the preceding claims, wherein the VEGF antagonist comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.
8. The VEGF antagonist for use according to any one of the preceding claims, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.
9. The VEGF antagonist for use according to claim 8, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
10. The VEGF antagonist for use according to claim 9, wherein the intraocular administration is intravitreal administration.
11. The VEGF antagonist for use according to claim 10, wherein all doses of the VEGF antagonist comprise from 0.5 mg to 2 mg of the VEGF antagonist.
12. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.
13. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

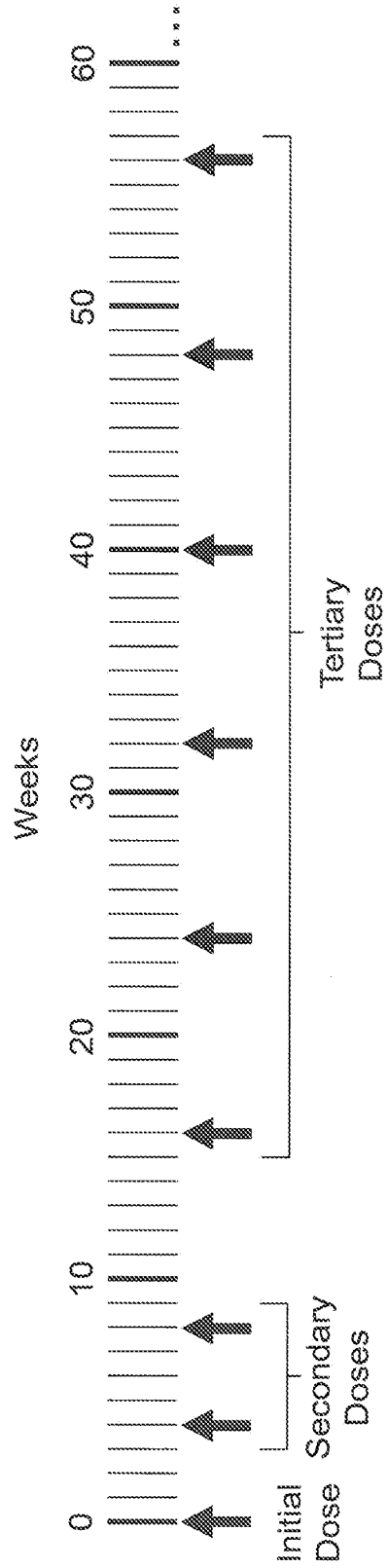


Figure 1



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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                       |                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Category                                                                                                                                                                                                                                                              | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                                                                                                                         | Relevant to claim                                                                                                                                                                                                                                                                                     | CLASSIFICATION OF THE APPLICATION (IPC)                     |
| X                                                                                                                                                                                                                                                                     | <p>Regeneron: "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration", Regeneron.com</p> <p>22 November 2010 (2010-11-22), XP002770953,<br/>Retrieved from the Internet:<br/>URL:http://investor.regeneron.com/releasedetail.cfm?releaseid=532099<br/>[retrieved on 2017-10-09]<br/>* the whole document *</p>                                       | 1,2,7-13                                                                                                                                                                                                                                                                                              | INV.<br>A61K38/18<br>A61P27/00                              |
| X                                                                                                                                                                                                                                                                     | <p>Regeneron: "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)", regeneron.com</p> <p>20 December 2010 (2010-12-20), XP002770954,<br/>Retrieved from the Internet:<br/>URL:http://investor.regeneron.com/releasedetail.cfm?releaseid=537916<br/>[retrieved on 2017-06-09]<br/>* the whole document *</p> | 1,4,7-13                                                                                                                                                                                                                                                                                              | <p>TECHNICAL FIELDS SEARCHED (IPC)</p> <p>A61K<br/>A61P</p> |
| X                                                                                                                                                                                                                                                                     | <p>RP: "VEGF Trap", retinalphysician.com</p> <p>1 March 2010 (2010-03-01), XP002770951,<br/>Retrieved from the Internet:<br/>URL:http://www.retinalphysician.com/issues/2010/march-2010/subspecialty-news<br/>[retrieved on 2017-06-09]<br/>* the whole document *</p> <p style="text-align: center;">-/-</p>                                                                                                                         | 1,7-13                                                                                                                                                                                                                                                                                                |                                                             |
| The present search report has been drawn up for all claims                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                       |                                                             |
| Place of search<br><b>Munich</b>                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                       | Date of completion of the search<br><b>12 June 2017</b>                                                                                                                                                                                                                                               | Examiner<br><b>Rodrigo-Simón, Ana</b>                       |
| <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone<br/>Y : particularly relevant if combined with another document of the same category<br/>A : technological background<br/>O : non-written disclosure<br/>P : intermediate document</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>T : theory or principle underlying the invention<br/>E : earlier patent document, but published on, or after the filing date<br/>D : document cited in the application<br/>L : document cited for other reasons<br/>.....<br/>&amp; : member of the same patent family, corresponding document</p> |                                                             |

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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                       |                                         |
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| Category                                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                                                                                                                                                                            | Relevant to claim                                                                                                                                                                                                                                                                     | CLASSIFICATION OF THE APPLICATION (IPC) |
| X                                                                                                                                                                                                                                                      | WO 00/75319 A1 (REGENERON PHARMA [US]; PAPADOPOULOS NICHOLAS J [US]; DAVIS SAMUEL [US]) 14 December 2000 (2000-12-14)<br>* page 87, line 14 - line 88 *<br>* page 14, line 7 - line 12 *                                                                                                                                                                                                                                                                                                 | 3,5,6                                                                                                                                                                                                                                                                                 | TECHNICAL FIELDS SEARCHED (IPC)         |
| X                                                                                                                                                                                                                                                      | US 2006/058234 A1 (DALY THOMAS J [US] ET AL) 16 March 2006 (2006-03-16)<br>* paragraph [0067] *<br>* claim 23 *<br>* page 2, paragraph 15 *                                                                                                                                                                                                                                                                                                                                              | 3                                                                                                                                                                                                                                                                                     |                                         |
| X                                                                                                                                                                                                                                                      | US 2005/260203 A1 (WIEGAND STANLEY J [US] ET AL) 24 November 2005 (2005-11-24)<br>* page 7; example 8 *<br>* page 8; example 9 *<br>* page 8; example 11 *<br>* page 9; example 2 *                                                                                                                                                                                                                                                                                                      | 3                                                                                                                                                                                                                                                                                     |                                         |
| X                                                                                                                                                                                                                                                      | NGUYEN Q D ET AL: "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration", OPHTHALMOLOGY, J. B. LIPPINCOTT CO., PHILADELPHIA, PA, US, vol. 116, no. 11, 1 November 2009 (2009-11-01), pages 2141-2148.E1, XP026732998, ISSN: 0161-6420, DOI: 10.1016/J.OPHTHA.2009.04.030 [retrieved on 2009-08-22]<br>* abstract *<br>* page 2142, column 1 - paragraph 3 *<br>* page 2147, column 1, paragraph 2 * | 3,5,6                                                                                                                                                                                                                                                                                 |                                         |
| The present search report has been drawn up for all claims                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                       |                                         |
| Place of search<br>Munich                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Date of completion of the search<br>12 June 2017                                                                                                                                                                                                                                      | Examiner<br>Rodrigo-Simón, Ana          |
| CATEGORY OF CITED DOCUMENTS<br>X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>.....<br>& : member of the same patent family, corresponding document |                                         |

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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                       |                                         |
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| Category                                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                                                                                                                          | Relevant to claim                                                                                                                                                                                                                                                                     | CLASSIFICATION OF THE APPLICATION (IPC) |
| X                                                                                                                                                                                                                                                      | DO DV ET AL.: "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema.",<br>BR J OPHTHALMOL,<br>vol. 93, no. 2, February 2009 (2009-02),<br>pages 144-149, XP009158490,<br>* abstract *<br>* page 149, paragraph 2 *<br>-----                                                                     | 3,5,6                                                                                                                                                                                                                                                                                 |                                         |
| X                                                                                                                                                                                                                                                      | ANANT PAI ET AL.: "Current concepts in intravitreal drug therapy for diabetic retinopathy",<br>SAUDI JOURNAL OF OPHTHALMOLOGY,<br>vol. 24, no. 4, 30 June 2010 (2010-06-30),<br>pages 143-149, XP002674122,<br>* page 147, paragraph 4 *<br>-----                                                                                                                                                                                      | 3                                                                                                                                                                                                                                                                                     |                                         |
| X                                                                                                                                                                                                                                                      | Regeneron Pharmaceuticals, Bayer, New York University: "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting",<br>Evaluate.com<br><br>28 September 2008 (2008-09-28),<br>XP002770952,<br>Retrieved from the Internet:<br>URL:http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=165320<br>[retrieved on 2017-06-09]<br>* the whole document *<br>-----<br>-/-- | 3,5,6                                                                                                                                                                                                                                                                                 | TECHNICAL FIELDS SEARCHED (IPC)         |
| The present search report has been drawn up for all claims                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                       |                                         |
| Place of search<br><b>Munich</b>                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                        | Date of completion of the search<br><b>12 June 2017</b>                                                                                                                                                                                                                               | Examiner<br><b>Rodrigo-Simón, Ana</b>   |
| CATEGORY OF CITED DOCUMENTS<br>X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document |                                                                                                                                                                                                                                                                                                                                                                                                                                        | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>.....<br>& : member of the same patent family, corresponding document |                                         |

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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                              |                                         |
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| Category                                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                               | Relevant to claim                                                                                                                                                                                                                                                            | CLASSIFICATION OF THE APPLICATION (IPC) |
| X                                                                                                                                                                                                                                                      | US 2007/190058 A1 (SHAMS NAVEED [US])<br>16 August 2007 (2007-08-16)<br>* claim 1 *<br>* paragraph [0112] *<br>* page 12, paragraph 111 *                                                                                                                                                                                                   | 3,5,6                                                                                                                                                                                                                                                                        |                                         |
| X                                                                                                                                                                                                                                                      | anonymous: "LUCENTIS® (ranibizumab injection) Intravitreal Injection",<br>June 2006 (2006-06), pages 1-3,<br>XP002674125,<br>Retrieved from the Internet:<br>URL:http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf<br>[retrieved on 2012-04-18]<br>* the whole document *                                          | 3,5,6                                                                                                                                                                                                                                                                        |                                         |
| X                                                                                                                                                                                                                                                      | Hailton B Oliveira ET AL: "VEGF Trap(R1R2) suppresses experimental corneal angiogenesis",<br>European journal of ophthalmology,<br>1 January 2010 (2010-01-01), page 48,<br>XP055328439,<br>Italy<br>Retrieved from the Internet:<br>URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3709022/pdf/nihms485251.pdf<br>* the whole document * | 6                                                                                                                                                                                                                                                                            |                                         |
| X                                                                                                                                                                                                                                                      | US 2006/172944 A1 (WIEGAND STANLEY J [US] ET AL) 3 August 2006 (2006-08-03)<br>* paragraphs [0008], [0017] *<br>* claims 1,2 *                                                                                                                                                                                                              | 3,5,6                                                                                                                                                                                                                                                                        |                                         |
| The present search report has been drawn up for all claims                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                              |                                         |
| Place of search<br>Munich                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                             | Date of completion of the search<br>12 June 2017                                                                                                                                                                                                                             | Examiner<br>Rodrigo-Simón, Ana          |
| CATEGORY OF CITED DOCUMENTS<br>X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document |                                                                                                                                                                                                                                                                                                                                             | T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>& : member of the same patent family, corresponding document |                                         |

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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                       |                                         |
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| Category                                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                      | Relevant to claim                                                                                                                                                                                                                                                                     | CLASSIFICATION OF THE APPLICATION (IPC) |
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