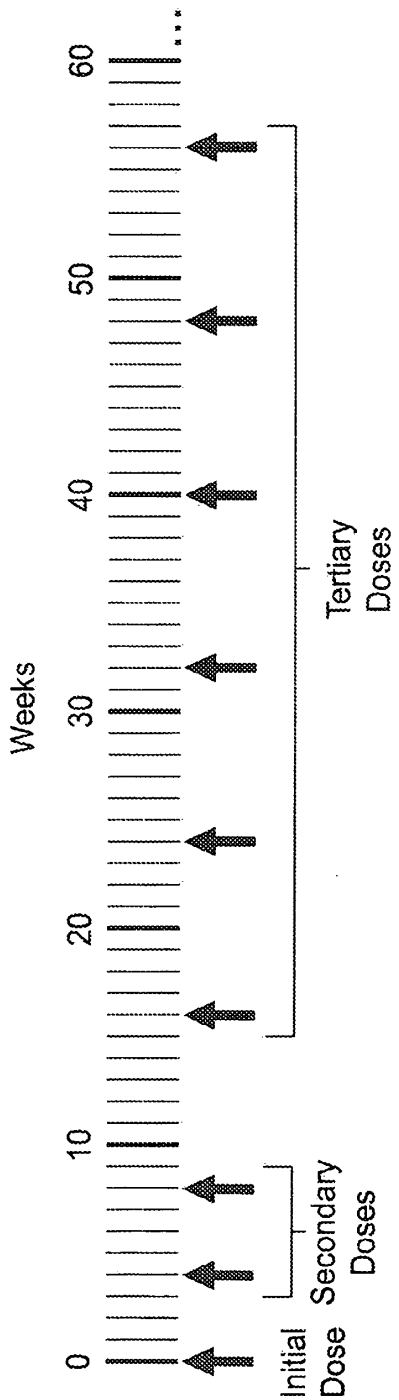

Figure 1

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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

[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 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

[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 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 (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following 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

[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 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

[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 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 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 ≥100 μm 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 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as 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:

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058]

C. Results Summary (52 Week Data)

[0059] 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[a] (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)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0060] 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.

[0061] 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)

[0062] 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[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0063] 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

[0064] 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

[0065] 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 ≥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.

[0066] At Week 24, 56.1% of VEGFT-treated patients gained ≥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 ≥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 µm for VEGFT-treated patients vs -381.8 µm 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.

[0067] 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

[0068] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTC
ACAGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCC
CCGAAATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTCAC
CTAACATCACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGC
ATAATCTGGGACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGC
TTCTGACCTGTGAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGA
CAAACCAATACAATCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGG
AGAAAAGCTTGTCTTAAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACT
GGGAATACCCTTCTTCGAAGCATCAGCATAAGAAACTTGTAAACCGAGACCTAAAAACCCA
GTCTGGGAGTGAGATGAAGAAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGT
GACCAAGGATTGTACACCTGTGCAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACA
TTTGTCAGGGTCCATGAAAAGGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAA
CTCCTGGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATC
TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG
AGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT

GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG
ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0069] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITV
TLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLS
PSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLT
IDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

[0070] 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.

What is claimed is:

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 claim 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 claim 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 claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 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 claim 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 claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 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 claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 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 claim 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 claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 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 claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 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 claim 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 claim 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 claims 21 to 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. The VEGF antagonist of any one of claims 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 claims 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 claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. The VEGF antagonist of any one of claims 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 claim 28, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

30. The VEGF antagonist of claim 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 claim 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 claims 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 claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

34. The VEGF antagonist of claim 33, wherein the intraocular administration is intravitreal administration.

35. The VEGF antagonist of claim 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 claim 35, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

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

ABSTRACT

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

Re Item II

Priority

1 The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (13.01.2011). It is to be noted that if the priority is not confirmed, D10 (XP002674122) would be relevant for novelty and inventive step of the claimed subject-matter (see point 8).

Re Item V

Reasoned statement under Rule 43bis1(a)(i) with regard to novelty, inventive step or industrial applicability.

2 **Nomenclature remarks (synonyms):** EYLEA, Aflibercept, VEGFR1R2-Fc [Delta]C1 (a), Zaltrap, AVE-0005, BAY-86-5321, NSC-724770, VEG Trap (R1R2), VEGF Trap and VEGF Trap-Eye.

3 **Claims 1-37** relate to the subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

4 **CLARITY, SUPPORT AND SUFFICIENCY OF DISCLOSURE (Arts. 5 and 6 PCT):**

4.1 **Claims 1-37** do not meet the requirements of Art. 6 PCT because attempt to define the therapeutic compound in terms of the result to be achieved "**VEGF antagonist**".

It appears possible to define the subject-matter in more concrete terms, viz. in terms how the effect is to be achieved, i.e. specific substances or compounds which antagonise VEGF, defined in technical terms (i.e. by means of their chemical structure/ aminoacidic sequence).

Claims 1-37 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function, i.e. antagonist VEGF effect, have not been described.

In the absence of such relationship either disclosed in the application as originally filed or which would have been recognised based on information readily available to the skilled person, the skill person would not know how to make and use compounds that lack any structural definition. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds, contrary to the requirements of Art. 5 PCT.

Claims 1-37 lack therefore clarity, support and disclosure, since the skilled person, after reading the description, would not be able to perform the invention over the whole area claimed without undue burden and without needing inventive skill (Arts. 5 and 6 PCT).

The present application does not provide examples of VEGF antagonists other than the compound known as VEGFR1R2-Fc [Delta]C1(a) (P.2, §9).

It seems that these objections would be overcome by defining the VEGF antagonist in the claims as consisting in (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1).

4.2 **Claims 1-5, 8-25 and 28-37** are additionally not in accordance with Art. 6 PCT because the therapeutic indication "**angiogenic eye disorder**" is vague and not clear. The skilled person is not necessarily aware of which diseases fall under this non-generally accepted therapeutic definition.

This objection could be overcome by specifying the angiogenic eye disorders as in claims 6-7 and 26-27, i.e. age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

4.3 **In view of the above objections no complete examination for the subject-matter of claims 1-37 can be carried out. However, for the sake of completeness and for the purpose of this examination only, the following comments on novelty and inventive step are made on these claims.**

5 **The following prior art documents have been taken into consideration:**

D1: US2007190058

D2: US2006172944

D3: US2005163798

D4: WO0075319

D5: US2006058234

D6: US2005260203

D7: XP26732998

D8: XP009158490

D9: XP002674122

D10: XP002674123

D11: XP002674124

D12: XP002674125

D13: XP002674126

D1 describes the treatment of (wet form) age-related macular degeneration in a mammal, comprising the steps of: a) administering to the mammal a number of first individual doses of an VEGF antagonist; and b) administering to the mammal a number of second individual doses of the VEGF antagonist, wherein the second individual doses are administered less frequently than the first individual doses (claim 1). The preferred VEGF antagonist is Ranibizumab (§112). In example 1 (Fig.1), the administration regime of the VEGF antagonist is every month (Day 0, Month 1 and 2) followed by seven doses every 3 months (P.12,§111).

D2 describes the use of VEGFR1R2-Fc [Delta]C1(a) for the treatment of eye injuries by reducing angiogenesis (§8,17 and claims1-2). The examples show the effect on sutured mice (i.e injury) but not on angiogenic eye disorders.

D3 describes that the fusion protein of SEQ.12 (claim 65; VEGFR1R2-Fc [Delta]C1(a) is useful in the treatment of eye disorders as age macular degeneration and diabetic retinopathy (§122). These uses are however the selection of two lists (compounds and diseases).

D4 describes chimeric polypeptides such as VEGFR1R2-Fc [Delta]C1(a) (P. 87, L.14-88) which are meant to inhibit vascular permeability for attenuation of edema above others (P.14, L7-12).

D5 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.7-8; §67) for the treatment of age related macular degeneration and diabetic retinopathy (claim 23). These conditions are known to be improved by inhibition or reduction of VEGF, which induce undesirable plasma leakage, vascular permeability or undesirable blood vessel growth (P.2, §15).

D6 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.6; claim 4) for the treatment of age related macular degeneration or diabetic retinopathy (claim 5). In D6, the examples show that VEGFR1R2-Fc [Delta]C1(a) has anti-angiogenic properties in induced ischemic retinopathy (P.7, Ex.8) and suppressed 70% of choroidal neovascularization when injected 2, 5, 8, and 11 days after laser treatment (animal model of AMD through laser disruption of Brunch's membrane) (P.8, Ex.9). Additionally, VEGFR1R2-Fc [Delta]C1(a) reduced the pathologic breakdown of the blood retinal barrier (P.8, Ex.11) and the infiltration of neutrophils and macrophages into the damaged cornea (P.9, Ex.2).

D7 (phase I; study with 21 patients), describes the improvement of best corrected visual acuity and the decrease of excess foveal thickness in patients with neovascular age-related macular degeneration patients treated with a single intravitreal injection of VEGF Trap-Eye (2-4mg).

D8 (preliminary study with 6 patients) describes that a single intravitreal injection of VEGF Trap-Eye (2mg) was well tolerated in patients with neovascular age-related macular degeneration (Abstract). The authors conclude that additional testing is to be performed by repeated injections at an interval of 6 weeks or longer (P.149, §2).

D9 describes the use of VEGF-tap-eye for the treatment of diabetic retinopathy (P.147, §4).

D10 (see point 7)

D11 (T-doc) reviews the known VEGF inhibitors used in ophthalmology.

D12 describes the recommended Lucentis® (Ranibizumab) dose 0.5mg to be administered by intravitreal injection once a month in the treatment of (wet) age-related macular degeneration.

D13 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule.

The phase III VEGF Trap-Eye trial methodology is described in D13 but no results are provided in this document. For this reason, the cited passage of D13 cannot be considered as an enabling disclosure of the presently claimed subject-matter. It is furthermore to be noted that the results of this phase III trial are indeed part of the experimental evidence provided in the present application (i.e. example 4 of the present application).

6 **NOVELTY (Arts. 33(1) and (2) PCT):**

Notwithstanding the above objections, the **subject-matter of claims 1-37 is novel** in the sense of Arts. 33(1) and (2) PCT because the specific administration regime of the claimed compounds has not been found to be disclosed in the prior art at hand.

7 **INVENTIVE STEP (Arts. 33(1) and (3) PCT):**

Notwithstanding the above objections, the subject-matter of **claims 1-37 is not inventive** because:

7.1 **The closest prior art, D13** (phase II study summary), describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by 40 additional weeks treatment on a PNR (as needed) dosing schedule.

7.2 **The difference** with D13 lies in that the present application provides the following:

7.2.1 **Compound** (i.e.VEGF antagonist):

(a) 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 (claims 8 and 28)

(b) VEGF antagonist is a VEGF receptor-based chimeric molecule (claims 9 and 29), a VEGF receptor-based chimeric molecule which comprises VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID N0:1 (claims 10 and 30) or a - 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 1D NO:2; and (3) a multimerization component comprising aminoacids 232-457 of SEQ.ID.2 (claims 11 and 31)

(c) the VEGF antagonist being VEGFR1R2-Fc [Delta]C1(a) (P.2, §9)

Administration regime of the above compounds:

- a single initial dose of, followed by one or more secondary doses, followed by one or more tertiary doses; 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

7.3 **The problem to be solved** lies in the provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.

7.4 **There are different solutions** provided by the claims which are directed to the administration of compounds (a)-(c) in a single initial dose, followed by one or more secondary doses, followed by one or more tertiary doses; 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; wherein:

a) 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 (claims 8 and 28) **(Solution 1)**

(b) VEGF antagonist is a VEGF receptor-based chimeric molecule (claims 9 and 29), a VEGF receptor-based chimeric molecule which comprises VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID N0:1 (claims 10 and 30) or a - 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 1D NO:2; and (3) a multimerization component comprising aminoacids 232-457 of SEQ.ID.2 (claims 11 and 31) **(Solution 2)**

(c) the VEGF antagonist being VEGFR1R2-Fc [Delta]C1(a) (SEQ.1)(P.2, §9) **(Solution 3)**

7.5 **In support of an inventive step** the applicant has provided the following examples:

Ex.1: a single intravitreal injection of VEGFT in neovascular AMD subjects resulted in reduction of pathological retinal thickness.

Ex.2: intravitreal injection of VEGFT every 4 or 12 weeks in neovascular AMD subjects resulted in increase of visual acuity.

Ex.3: four injections of VEGFT over an 8-week period resulted in improved visual acuity.

Ex.5: patients with diabetic macular edema which were eligible for laser treatments showed gain in visual acuity when treated with VEGFT (Table 2).

Ex.6: naive patients with macular edema secondary to central retinal vein occlusion treated with 6 monthly intravitreal VEGFT injections showed improvement of visual acuity at week 24 which was maintained through week 52.

7.5.1 The most relevant example for the claimed subject-matter seems to be **Ex.4** where VEGFT demonstrated non-inferiority of efficacy compared to Ranibizumab.

In this example, VEGFT was administered every 4 weeks (1Q4 and 0,5Q4) or every 4 weeks to week 8 with additional administrations every 8 weeks (2Q8) (Fig.1). The effects after 52 weeks treatment are summarised in Table 1 where it is shown that the claimed administration protocol achieved similar effect than 0,5mg Ranibizumab monthly administered (non-inferiority statistical analysis).

It is to be noted that the applicant refers in the examples to the used compound as "VEGFT". However, in P.2, §9 is indicated that, the VEGFT is VEGFR1R2-Fc [Delta]C1(a) (i.e.VEGF Trap-Eye). It is therefore to be considered that the "VEGFT" meant in the present examples is indeed VEGFR1R2-Fc [Delta]C1(a). Additionally, in D7, which is the scientific publication of the results of the present Ex.1, the used compound is VEGFR1R2-Fc [Delta]C1(a).

In summary, the above results can only be attributed to the specific VEG antagonist being (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1).

7.5.2 **Generalisation to the disclosed angiogenic eye disorders:**

It is to be noted that the technical effect shown is limited to macular degeneration. The generalisation to the treatment of diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization is however possible because these eye disorders have in common a process of pathogenic angiogenesis which is plausibly expected to be successfully treated with the provided VEGFR1R2-Fc [Delta]C1(a) protocol.

7.5.3 **Generalisation to any VEGF antagonist not possible:**

This effect cannot be generalised to any compound which could fall under the functional definition "VEGF antagonist" in general or under the VEGF antagonist as defined in (a)-(c) (see point 7.2 above). This generalisation is not possible because each antagonist (as above defined) has different nature (i.e. tridimensional structure, half life, binding affinity, etc.) and therefore different antagonistic effect. In summary, the above VEGF antagonists are not necessarily expected to achieve the effect shown for VEGFR1R2-Fc [Delta]C1 (a) (SEQ.1) when administered as claimed.

The technical effect of any VEGF antagonist in general or as defined in (a)-(c) (i.e. Solutions 1-2), cannot be acknowledged.

A technical effect solving a technical problem has to be achieved by all embodiments falling within the scope of the claims. Claims covering embodiments not achieving such effect, not shown to have achieved such effect are considered not to solve the underlying technical problem. These claims are therefore not inventive.

7.6 Starting from the closest prior art, D13, **any VEGF antagonist as defined in a-c (i.e. Solutions 1-2)** administered in a single initial, followed by one or more secondary doses, followed by one or more tertiary doses; 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 **are obvious non-inventive solutions** for use in the treatment of age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization because their technical effect has not been demonstrated (i.e. the problem has not been shown to be solved over the whole scope).

7.7 **Claims 1-37 are not in accordance with the requirements of Arts. 33(1) and (3) PCT.**

7.8 The attention of the applicant is drawn to the fact that the technical effect of the claimed protocol, wherein the VEG antagonist is VEGFR1R2-Fc [Delta]C1 (a) (SEQ.1) has been demonstrated in the present application (Solution 3).

Starting from the closest prior art, D13, the VEGF antagonist consisting in/ being **VEGFR1R2-Fc [Delta]C1(a)** (SEQ.1) administered in a single initial, followed by one or more secondary doses, followed by one or more tertiary

doses; 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 is a **non-obvious and inventive solution** for use in the treatment of age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization becuase its technical effect has been demonstrated (i.e. plausibly solving the problem over the whole scope). The skilled person would have not come to this solution without inventive skill.

Re Item VI

Certain documents cited

8 **D10** (XP002674122) describes the results of the present example 5. The administration schedule in Fig.1 "2mg q8 wks" is the same than in the present claims.

This document could become relevant for the assessment of novelty and inventive step if the priority date 13.01.2011 is not confirmed.

Re Item VIII

9 **Certain observations on the international application Clarity (Art.6 PCT):**

See point 4.

10 **AMENDMENTS**

10.1 The attention of the applicant is drawn to the fact that, notwithstanding the above comments to the partial subject-matter of this application which could be regarded as being in accordance **with Arts.5, 6 and 33(1) and (3) PCT, it is the applicant's sole responsibility to amend the application documents in accordance with Art.34 or Art.19 PCT.**

10.2 **When /if carrying amendments**, and in order to facilitate the examination of the conformity of the amended application with the requirements of Article 34 (2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate precisely the passages of the application as filed on which these amendments are based (also Rule 66.8 (a) PCT).

Only amendments with a clearly identified basis on the application as originally filed will be taken into account for the international preliminary examination report.

10.3 **If this application enters in the regional phase**, it is to be noted that claims referred to methods of treatment are not patentable pursuant to Art.53(c) EPC. The allowable wording for further medical use claims according to the EPC2000 is the following:

Independent claim: "Compound x for use in the treatment of disease y"

Dependent claims: "Compound x for use according to claim a, wherein..."

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2012/020855	11.01.2012	13.01.2011

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/18 A61P27/00

Applicant
REGENERON PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Rodrigo-Simón, Ana Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☒ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2012/097019 A1

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

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

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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

[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 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

[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 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 (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following 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

[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 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

[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 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 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 ≥100 μm 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 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as 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:

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058]

C. Results Summary (52 Week Data)

[0059] 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[a] (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)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0060] 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.

[0061] 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)

[0062] 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[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0063] 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

[0064] 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

[0065] 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 ≥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.

[0066] At Week 24, 56.1% of VEGFT-treated patients gained ≥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 ≥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 µm for VEGFT-treated patients vs -381.8 µm 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.

[0067] 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

[0068] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

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GTCTGGGAGTGAGATGAAGAAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGT
GACCAAGGATTGTACACCTGTGCAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACA
TTTGTCAGGGTCCATGAAAAGGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAA
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CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG
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ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG
ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
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[0069] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITV
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PSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLT
IDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK

[0070] 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.

What is claimed is:

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 claim 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 claim 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 claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 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 claim 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 claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 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 claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 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 claim 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 claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 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 claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 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 claim 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 claim 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 claims 21 to 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. The VEGF antagonist of any one of claims 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 claims 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 claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. The VEGF antagonist of any one of claims 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 claim 28, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

30. The VEGF antagonist of claim 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 claim 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 claims 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 claim 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

34. The VEGF antagonist of claim 33, wherein the intraocular administration is intravitreal administration.

35. The VEGF antagonist of claim 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 claim 35, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

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

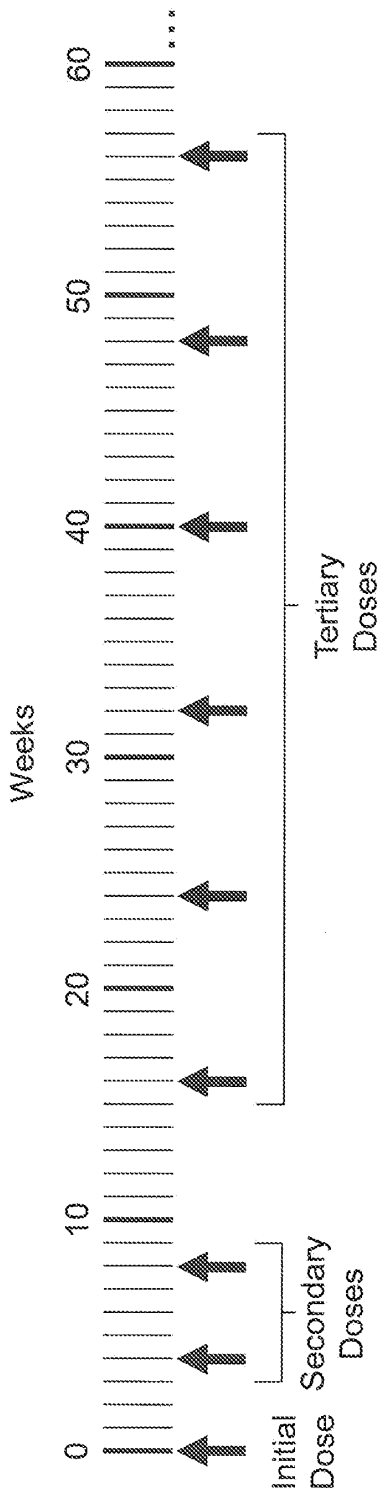
Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/020855

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/18 A61P27/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Thomson Reuters Integrity: "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting", , 28 September 2008 (2008-09-28), pages 1-1, XP002674126, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_llist at_refs?p_session_id=1868065&p_orig=&p_count=354&p_num_dailys=42&p_qry_save=&p_subtitol=Biomedical%20Literature%20List&p_dailys=N&p_tsearch=A&p_text=N&p_whatToShow=REF&p_prousQuantity=5&p_page=10#link [retrieved on 2012-04-18] the whole document ----- -/--	1-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2012	22/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rodrigo-Simón, Ana

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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1

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Information on patent family members

International application No
PCT/US2012/020855

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SEQUENCE LISTING

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

<130> 725A-WO

<140> To be assigned
<141> Filed herewith

<150> 61/432,245
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        35                  40                  45
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    50                  55                  60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65                  70                  75                  80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
                85                  90                  95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
            100                 105                 110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
        115                 120                 125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
    130                 135                 140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145                 150                 155                 160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
                165                 170                 175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
            180                 185                 190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
        195                 200                 205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
    210                 215                 220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                245                 250                 255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            340                 345                 350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
        355                 360                 365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    370                 375                 380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385                 390                 395                 400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                405                 410                 415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            420                 425                 430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        435                 440                 445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455
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USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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] Current 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)."

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

BRIEF DESCRIPTION OF THE FIGURE

[0010] 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

[0011] 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.

[0012] 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.).

[0013] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

DOSING REGIMENS

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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

[0020] 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.

[0021] 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").

[0022] 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.

[0023] 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

[0024] 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

[0025] 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.

[0026] 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

[0027] 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

[0028] 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.

[0029] 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.

[0030] 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

[0031] 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 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

[0032] 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 degrees Centigrade, and pressure is at or near atmospheric.

[0033] 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 (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following 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

[0034] 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 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

[0035] 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 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 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

[0036] 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.

[0037] 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

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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

[0042] 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).

[0043] 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 ≥100 μm 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.

[0044] 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.

[0045] Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

[0046] 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.

[0047] 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.

[0048] 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).

[0049] 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 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial

tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as 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.

[0050] 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.

[0051] The study procedures are summarized as follows:

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057]

C. Results Summary (52 Week Data)

[0058] 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[a] (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)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0059] 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.

[0060] 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)

[0061] 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[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0062] 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

[0063] 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

[0064] 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 ≥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.

[0065] At Week 24, 56.1% of VEGFT-treated patients gained ≥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 ≥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 µm for VEGFT-treated patients vs -381.8 µm 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.

[0066] 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

[0067] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTCAC
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAAACTTGTAAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0068] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGI
ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0069] 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.

What is claimed is:

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 claim 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 claim 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 claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 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 claim 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 claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 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 claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 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 claim 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 claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 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 claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

ABSTRACT

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

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

PTO/SB/16 (09-11)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. (filed via EFS Web)

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
George D.	Yancopoulos	Yorktown Heights, NY

Additional inventors are being named on the 0 *separately numbered sheets attached hereto.*

TITLE OF THE INVENTION (500 characters max):

Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ The address corresponding to Customer Number: 26693

OR

☐ Firm or Individual Name

Address

City	State	Zip
Country	Telephone	Email

ENCLOSED APPLICATION PARTS ***(check all that apply)***

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number of CDs

☒ Drawing(s) *Number of Sheets* 1

☐ Other (specify)

☒ Specification (e.g. description of the invention) *Number of Pages* 22

Fees Due: Filing Fee of $250 ($125 for small entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order made payable to the *Director of the United States Patent and Trademark Office* is enclosed to cover the filing fee and application size fee (if applicable).

☐ Payment by credit card. Form PTO-2038 is attached.

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☒ The Director is hereby authorized to charge the filing fee and application size fee (if applicable) or credit any overpayment to Deposit Account Number: 18-0650

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SIGNATURE Frank R. Cottingham Date November 21, 2011

TYPED or PRINTED NAME Frank R. Cottingham REGISTRATION NO. 50,437 *(if appropriate)*

TELEPHONE 914-593-1116 (direct) Docket Number: _____

Electronic Acknowledgement Receipt	
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Application Number:	61561957
International Application Number:	
Confirmation Number:	8366
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First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	26693
Filer:	Frank Robert Cottingham
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	21-NOV-2011
Filing Date:	
Time Stamp:	09:08:10
Application Type:	Provisional

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	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	19	
	Claims		20	21	
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2	Drawings-only black and white line drawings	Figure1.pdf	17039 945457aa6d8cc57408af1b15f9b29373a0f30ae1c	no	1
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USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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] Current 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)."

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

BRIEF DESCRIPTION OF THE FIGURE

[0010] 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

[0011] 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.

[0012] 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.).

[0013] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

DOSING REGIMENS

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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

[0020] 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.

[0021] 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").

[0022] 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.

[0023] 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

[0024] 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

[0025] 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.

[0026] 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

[0027] 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

[0028] 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.

[0029] 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.

[0030] 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

[0031] 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 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

[0032] 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 degrees Centigrade, and pressure is at or near atmospheric.

[0033] 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 (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following 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

[0034] 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 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

[0035] 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 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 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

[0036] 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.

[0037] 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

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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

[0042] 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).

[0043] 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 ≥100 μm 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.

[0044] 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.

[0045] Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

[0046] 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.

[0047] 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.

[0048] 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).

[0049] 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 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial

tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as 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.

[0050] 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.

[0051] The study procedures are summarized as follows:

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057]

C. Results Summary (52 Week Data)

[0058] 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[a] (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)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0059] 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.

[0060] 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)

[0061] 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[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0062] 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

[0063] 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.

SEQUENCES

[0064] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTCAC
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAAACTTGTAAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0065] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGI

ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0066] 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.

What is claimed is:

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 claim 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 claim 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 claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 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 claim 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 claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 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 claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 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 claim 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 claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 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 claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

ABSTRACT

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

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

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Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
Attorney Docket Number (if applicable)	725P

Correspondence Address

Direct all correspondence to (select one):

(•) The address corresponding to Customer Number	( ) Firm or Individual Name
Customer Number	26693

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

(•) No.

( ) Yes, the name of the U.S. Government agency and the Government contract number are:

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Signature	Frank R. Cottingham			Date (YYYY-MM-DD)	2011-01-13
First Name	Frank	Last Name	Cottingham	Registration Number (If appropriate)	50437

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USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

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] Current 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)."

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

BRIEF DESCRIPTION OF THE FIGURE

[0010] 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

[0011] 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.

[0012] 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.).

[0013] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

DOSING REGIMENS

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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

[0020] 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.

[0021] 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").

[0022] 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.

[0023] 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

[0024] 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

[0025] 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.

[0026] 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

[0027] 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

[0028] 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.

[0029] 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.

[0030] 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

[0031] 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 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

[0032] 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 degrees Centigrade, and pressure is at or near atmospheric.

[0033] 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 (VEGFR1R2-FcΔC1(a); encoded by SEQ ID NO:1). This VEGF antagonist is referred to in the examples below as "VEGFT". For purposes of the following 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

[0034] 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 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

[0035] 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 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 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

[0036] 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.

[0037] 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

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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

[0042] 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).

[0043] 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 ≥100 μm 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.

[0044] 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.

[0045] Approximately 1200 subjects were enrolled, with a target enrollment of 300 subjects per treatment arm.

[0046] 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.

[0047] 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.

[0048] 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).

[0049] 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 mm2, including blood, scars and neovascularization) as assessed by FA in the study eye. 5. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.) 6. Scar or fibrosis, making up > 50% of total lesion in the study eye. 7. Scar, fibrosis, or atrophy involving the center of the fovea. 8. Presence of retinal pigment epithelial

tears or rips involving the macula in the study eye. 9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye. 10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye. 11. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. 12. Prior vitrectomy in the study eye. 13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye. 14. Any history of macular hole of stage 2 and above in the study eye. 15. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as 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.

[0050] 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.

[0051] The study procedures are summarized as follows:

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057]

C. Results Summary (52 Week Data)

[0058] 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[a] (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)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS

[a] Following three initial monthly doses
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
*** Test for superiority
NS = non-significant

[0059] 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.

[0060] 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)

[0061] 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[a] (2Q8)	42	8.5**	9.7**
VEGFT 2 mg as needed[a] (PRN)	45	10.3**	12.0**

[a] Following three initial monthly doses
** $p < 0.01$ versus laser

[0062] 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

[0063] 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.

SEQUENCES

[0064] SEQ ID NO:1 (DNA sequence having 1377 nucleotides):

ATGGTCAGCTACTGGGACACCGGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTCAC
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAAACTTGTAAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTTGAGCACCTTAACTATAGATGGTGTAACCCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

[0065] SEQ ID NO:2 (polypeptide sequence having 458 amino acids):

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGI

ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0066] 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.

What is claimed is:

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 claim 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 claim 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 claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of claim 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 claim 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 claim 6, wherein the angiogenic eye disorder is age related macular degeneration.

8. The method of claim 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 claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

10. The method of claim 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 claim 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 claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

14. The method of claim 13, wherein the intraocular administration is intravitreal administration.

15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

17. The method of claim 16, wherein the intraocular administration is intravitreal administration.

18. The method of claim 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 claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

ABSTRACT

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

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

Figure 1

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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country
George	D.	Yancopoulos	Yorktown Heights	NY	US

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Title of Invention	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
Attorney Docket Number (if applicable)	725P1

Correspondence Address

Direct all correspondence to (select one):

(•) The address corresponding to Customer Number	( ) Firm or Individual Name
Customer Number	26693

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

(•) No.

( ) Yes, the name of the U.S. Government agency and the Government contract number are:

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Entity Status

Applicant claims small entity status under 37 CFR 1.27

○ Yes, applicant qualifies for small entity status under 37 CFR 1.27

◉ No

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Signature	Frank R. Cottingham			Date (YYYY-MM-DD)	2011-01-20
First Name	Frank	Last Name	Cottingham	Registration Number (If appropriate)	50437

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First Named Inventor/Applicant Name:	George D. Yancopoulos
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Reference	Application No./Patent No.
	12700590.8 - 1456 PCT/US2012020855
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Entry into the European phase before the European Patent Office

The following information describes the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read it carefully because failure to take the necessary action in due time can lead to a loss of rights.

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   During the European phase before the EPO as designated or elected Office, however, such applicants **must** be represented by a professional representative (Art. 133(2) and Art. 134(1) and (8) EPC).

   Where, at the expiry of the time period laid down in Rule 163(5) EPC, the requirements of Article 133(2) EPC have not been complied with, the European patent application will be **refused**, pursuant to Rule 163(6) EPC.

   Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise the EPO has to send all communications directly to the applicant.

3. Applicants **with a residence or their principal place of business** in an EPC Contracting State are not obliged to appoint for the European phase a professional representative authorised to act before the EPO. However, in view of the complexity of the procedure it is recommended that they do so.

4. Applicants and professional representatives are also strongly advised to initiate the European phase using **EPO Form 1200**. It is available free of charge from the EPO or via the EPO website at **www.epo.org**. Similarly, it can be or generated with the Online Filing software, obtainable free of charge from the EPO (**www.epoline.org**) The use of the form is not compulsory.

5. Where the EPO acts as designated or elected Office (Art. 22(1) and (3) and 39(1) PCT), to enter the European phase before the EPO, the **following acts** must be performed by the applicant within **31 months** from the date of filing of the international application or (where applicable) the earliest priority date:

   a) Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such language (Art. 22(1) PCT and R. 159(1)(a) EPC);

   b) Specify the application documents, as originally filed or as amended, on which the European grant procedure is to be based (R. 159(1)(b) EPC);

   c) Pay the filing fee and, where applicable, the additional fee for a European patent application comprising more than 35 pages (R. 159(1)(c) EPC, Art. 2, items 1, 1a Rules relating to Fees);

   d) Pay the search fee where a supplementary European search report has to be drawn up (R. 159(1)(e) EPC);

   e) Pay the designation fee if the time limit laid down in Rule 39(1) EPC (i.e. six months after publication of the international search report) has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(d) EPC);

   f) File the written request for examination and pay the examination fee if the time limit laid down in Rule 70(1) EPC has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(f) EPC);

   g) Pay the renewal fee in respect of the third year, if the fee has fallen due (see Rule 51(1) EPC) before expiry of the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(g) EPC);

   h) File, where applicable, the certificate of exhibition referred to in Article 55(2) and Rule 25 EPC (R. 159(1)(h) EPC);

   i) Pay the claims fees for the sixteenth and each subsequent claim when the application documents on which the European grant procedure is to be based comprise more than fifteen claims (R. 162(1) EPC). For applications entering the European phase on or after 1 April 2009, a higher amount is payable for the 51st and each subsequent claim (Decision of the Administrative Council of 14 December 2007 amending the Rules relating to Fees, OJ EPO 2008, 10).

   If either the translation of the international application or the request for examination is not filed in time, or if the filing fee, the additional fee, the search fee, the designation fee or the examination fee is not paid in due time, the application shall be deemed to be withdrawn (R. 160(1) EPC).

6. Payment of fees

   An up-to-date guidance for the payment of fees, expenses and prices and a list of the euro accounts of the European Patent Organisation are published in each issue of the Official Journal of the EPO. The guidance includes inter alia a reference to the latest version of the Schedule of fees and expenses where the amounts of fees are set out.

   The Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (**www.epo.org**) and can be found under **www.epo.org/schedule-of-fees**, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

   Applicants should always check the fee amounts applying at the time of payment.

Payments can be validly made by any person. Permissible methods of payment are laid down in Article 5 Rules relating to Fees. Please note that payment cannot be made by cheque sent to the EPO.

For information on the calculation of the additional fee for applications comprising more than 35 pages, see Notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 118), Notice supplementing the notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 338) and Guidelines for Examination in the EPO, April 2010, A-III, 13.2.

For an overview of search and examination fees, see Notice from the European Patent Office dated 8 February 2010 (OJ EPO 2010, 133). Fee information is also published on the EPO website under **www.epo.org/fees.**

7. Restoration of priority right

Where the international application contains a priority claim to an earlier application and it has been filed within two months from the expiration of the 12-month priority period, a request for restoration before the EPO as designated Office (R. 49*ter*.2 PCT) applies under the following circumstances:

a) No request for restoration filed before the receiving Office (RO) during the international phase (R. 26*bis*.3 PCT)
b) Negative decision by the RO irrespective of the criterion applied (due care/ unintentionality)
c) Positive decision by the RO based on the unintentionality criterion.

For a request to be admissible, it must be filed and the requisite fee must be paid (R. 49*ter*.2(b)(iii) and R. 49*ter*.2(d) PCT) within one month from the applicable time limit under Article 22 PCT for entering the regional phase (R. 49*ter*.2(b)(i) PCT). The request for restoration also needs to state the reasons for the failure to file the international application within the priority period (Rule 49*ter*.2(b)(ii) PCT).

8. If the applicant had appointed a representative during the application's international phase, the present Form will be sent to the representative, asking him to inform the applicant accordingly.
All subsequent communications will be sent to the applicant, or - if the EPO is informed of his appointment in time - to the applicant's European representative.

9. For more details about time limits and procedural acts before the EPO as designated or elected Office, see the EPO brochure "How to get a European patent", Guide for applicants - Part 2, PCT procedure before the EPO - "Euro-PCT".
This brochure, the list of professional representatives before the EPO as well as Form 1200 are available on the Internet under **www.epo.org**.

Receiving Section

Europäisches Patentamt
European Patent Office
Office européen des brevets

Entry into the European phase (EPO as designated or elected Office)

To the European Patent Office

European application number	EP12700590.8
PCT application number	PCT/US2012/020855
PCT publication number	WO2012097019
Applicant's or representative's reference	N400458-EP DXP
International Filing Date	11.01.2012
International Searching Authority (ISA)	EP
International Preliminary Examining Authority (IPEA)	not applicable

1. Applicant

Indications concerning the applicant(s) are contained in the international publication or were recorded by the International Bureau after the international publication. ☒

Changes which have not yet been recorded by the International Bureau are set out here: ☐

2. Representative

This is the representative who will be listed in the Register of European Patents and to whom notifications will be made

Representative 1

Name: POWER, Mr David

Company: J A Kemp

Address of place of business: 14 South Square
Gray's Inn

London , Greater London, WC1R 5JJ

United Kingdom

Telephone: +44 20 3077 8600

Fax: +44 20 7242 8932

e-mail: mail@jakemp.com

3. Authorisation

An individual authorisation is attached. ☐

A general authorisation has been registered under No: ☐

A general authorisation has been filed, but not yet registered. ☐

The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase. ☐

4. Request for examination

Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid. ☒

Request for examination in an admissible non-EPO language: ☐

The applicant waives his right to be asked under Rule 70(2) EPC whether he wishes to proceed further with the application. ☐

5. Copies

Additional copies of the documents cited in the supplementary European search report are requested. ☐

Number of additional sets of copies

6. Documents intended for proceedings before the EPO

Number of claims on entry into the European phase: 15

6.1 Proceedings before the EPO as designated Office (PCT I) are to be based on the following documents:

the application documents published by the International Bureau (with all claims, description and drawings), where applicable with amended claims under Art. 19 PCT ☐

unless replaced by the amendments attached.	☒
Where necessary, clarifications should be attached as `Other documents`	
6.2 Proceedings before the EPO as elected Office (PCT II) are to be based on the following documents:	
the documents on which the international preliminary examination report is based, including any annexes	☐
unless replaced by the amendments attached.	☐
Where necessary, clarifications should be attached as `Other documents`	
If the EPO as International Preliminary Examining Authority has been supplied with test reports, these may be used as the basis of proceedings before the EPO.	☐
6.3 A copy of the results of the search carried out by the authority with which the previous application(s) whose priority is claimed was (were) filed is attached (R. 141(1) EPC).	☐
6.4 The applicant waives his right to the communication under Rules 161(1) or (2) and 162 EPC.	☐
7. Translations	
Translations in one of the official languages of the EPO (English, French, German) are attached as crossed below:	☐
** In proceedings before the EPO as designated or elected Office (PCT I + II):*	
Translation of the international application (description, claims, any text in the drawings) as originally filed, of the abstract as published and of any indication under Rule 13bis.3 and 13bis.4 PCT regarding biological material	☐
Translation of the priority application(s) (to be filed only at the EPO's request, Rule 53(3) EPC)	☐
It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 53(3) EPC)	☐
** In addition, in proceedings before the EPO as designated Office (PCT I):*	
Translation of amended claims and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6).	☐
** In addition, in proceedings before the EPO as elected Office (PCT II):*	
Translation of annexes to the international preliminary examination report	☐
8. Biological material	
The invention uses and/or relates to biological material deposited under Rule 31 EPC.	☐
The particulars referred to in Rule 31(1)(c) EPC (if not yet known, the depositary institution and the identification reference(s)) [number, symbols, etc.] of the depositor) are given in the international publication or in the translation submitted in Section 7 on:	☐
page(s) / line(s)	
The receipt(s) of deposit issued by the depositary institution	
is (are) enclosed.	☐
will be filed later.	☐
Waiver of the right to an undertaking from the requester pursuant to Rule 33(2) EPC attached.	☐
9. Nucleotide and amino acid sequences	
The international application discloses nucleotide and/or amino acid sequences.	☒
9.1 The sequence listing was filed under Rule 5.2(a) PCT, or furnished to the EPO as ISA under Rule 13ter.1(a) PCT, or is otherwise available to the EPO, in computer-readable format in accordance with WIPO ST.25.	☒
9.2	
The sequence listing is attached in computer-readable format in accordance with WIPO Standard ST.25	☐
The sequence listing is attached in PDF format.	☐
The sequence listing does not include matter which goes beyond the content of the application as filed.	☐
10. Designation fees	

All the contracting states party to the EPC at the time of filing of the international patent application and designated in the international application are deemed to be designated (see Article 79(1) EPC). ☒

The following states, which were contracting states to the EPC at the time of filing of the international application, are designated:

AL AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

11. Extension of the European patent

☐

This application is deemed to be a request to extend the European patent application and the European patent granted in respect of it to all the non-contracting states to the EPC designated in the international application and with which extension agreements are in force on the date on which the international application is filed. However, the extension only takes effect if the prescribed extension fee is paid.

It is currently intended to pay the extension fee for the following states:

Note: Under the automatic debiting procedure, extension fees will only be debited for states indicated here, unless the EPO is instructed otherwise before expiry of the period for payment.

12. List of enclosed documents

	Description of document	Original file name	Assigned file name
1	Combined Amendments	N400458EP DXP txb amended claims _clean_.pdf	AMSPECEPO-1.pdf
2	Amended claims with annotations	N400458EP DXP txb amended claims _tracked_.pdf	CLMS-HWA.pdf
3	cover letter	N400458EP DXP txb EP Regional Phase - Jun 13.pdf	OTHER-1.pdf

13. Mode of payment: Debit from deposit account

☒

Currency: EUR

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.

Deposit account number: 28050038

Account holder: J A Kemp

14. Any refunds should be made to the following EPO deposit account:

☒

Number and account holder: J A Kemp, 28050038

15. Fees

		Factor/reduction applied	Fee schedule	Amount to be paid
15-1	005e Designation fee - For all contracting States designated for applications filed on/after 01.04.2009	1	555.00	555.00
15-2	006e Examination fee - For applications filed before 01.07.2005 and for international applications filed on/after 01.07.2005 without supplementary European search report	1	1 730.00	1 730.00
15-3	020 Filing fee - entry EP phase - online	1	115.00	115.00
	Total:		EUR	2 400.00

16. Annotations

17. Signature(s) of applicant(s) or representative

Place: London

Date: 05 July 2013

Signed by: GB, J A Kemp & Co., D. Power 23473

Capacity: (Representative)

Table for section 6 of Form 1200.3

In accordance with the Notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 118, and Guidelines for Examination in the EPO, April 2009, A-III, 13.2), the amount of the additional fee (Art. 2, item 1a, Rules relating to Fees) for the pages of this European patent application is calculated as follows:

Documents intended for proceedings before the EPO (R. 159 (1) (b) EPC) and for calculating the additional fee (Art. 2, item 1a, RFees):

		Page(s) from ... to ...	Number of pages
Description:	International application as published	1 to 18	18
Claims:	Amendments filed on entry into European phase	19 to 20	2
Drawings:	International application as published	1/1 to 1/1	1
Abstract:	Default count: one page		1
Total number of pages			22
Fee-exempt pages (Art. 2, item 1a, RFees)			-35
Number of pages to be paid for			0
			(x 14 EUR per page)
Total amount payable		EUR	0

N400458-EP DXP

J A · KEMP

BY ONLINE FILING

The European Patent Office
Bayerstrasse 34
(entrance via Zollstrasse 3)
80335 Munich
Germany

5 July 2013

Dear Sirs

European Patent Application No. 12700590.8
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP DXP/txb

We request entry of the above-identified international application into the European regional phase and examination of the application under Article 94 EPC. We enclose EPO Form 1200.

We request that the following fees are deducted from J A Kemp's deposit account number 2805.0038:

- online filing fee (EUR 115);
- the designation fee for all possible EPC states (EUR 555); and
- the examination fee (EUR 1730).

No search fee is being paid as the EPO acted as the International Search Authority. We hereby authorise you to deduct the amount of any underpayment from, or credit the amount of any overpayment to, the above-identified deposit account.

We enclose:

1. A new set of claims.

2. A copy of the original claims showing the amendments in manuscript.

We request that EPO processing is carried out on the basis of the international application as published except for replacement of the claims with those attached.

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7242 8932
mail@jakemp.com www.jakemp.com

A list of our partners is available at our principal place of business at the address above. Regulated by IPREG

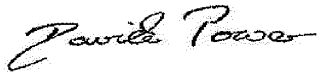
Amendments

The claims have been amended to reduce their overall number to 15. That has been achieved by cancelling previous claims 1 to 20 and also combining a number of the remaining claims.

New claim 15 has been added which is a "Swiss" format second medical use claim. Please note that the earliest priority date claimed by the present application is 21 January 2011 and hence prior to the 28 January 2011 cut-off for the inclusion Swiss format claims. It is therefore permissible to have a claim in that format in the present case. The claim essentially corresponds to original claims 1 and 21 of the application as filed, except for the conversion into a Swiss style claim, hence finds basis in those two original claims.

It is believed that the basis for the other amendments will be self-evident from the tracked version of the original claims.

Yours faithfully



DR DAVID POWER

CLAIMS – TRACKED VERSION

[1.] – [20.] Cancelled.

121. 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.

222. The VEGF antagonist of claim 21, wherein:

(a) 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.; or

(b) 23. The VEGF antagonist of claim 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.

324. The VEGF antagonist of any one of claims 21 toor 23, wherein:

(a) each tertiary dose is administered 8 weeks after the immediately preceding dose.; or

(b) 25. The VEGF antagonist of any one of claims 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.

426. The VEGF antagonist of any one of the preceding claims 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.

5.27. The VEGF antagonist of claim 426, wherein the angiogenic eye disorder is age related macular degeneration.

628. The VEGF antagonist of any one of the preceding claims 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.

729. The VEGF antagonist of claim 286, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

830. The VEGF antagonist of claim 729, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

931. The VEGF antagonist of claim 729, 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.

1032. The VEGF antagonist of any one of the preceding claims 21 to 31, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

1133. The VEGF antagonist of claim 1032, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

1234. The VEGF antagonist of claim 1133, wherein the intraocular administration is intravitreal administration.

1335. The VEGF antagonist of claim 1234, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

1436. The VEGF antagonist of claim 1335, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.; or

(b) 37. The VEGF antagonist of claim 35, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

15. Use of a VEGF antagonist in the manufacture of a medicament for use in a method of treating an angiogenic eye disorder in a patient, where the treatment 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.

CLAIMS

1. 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.

2. The VEGF antagonist of claim 1, wherein:

(a) 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; or

(b) only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

3. The VEGF antagonist of claim 1 or 2, wherein:

(a) each tertiary dose is administered 8 weeks after the immediately preceding dose; or

(b) 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.

4. The VEGF antagonist of any one of the preceding claims, 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.

5. The VEGF antagonist of claim 4, wherein the angiogenic eye disorder is age related macular degeneration.

6. The VEGF antagonist of any one of the preceding claims, 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.

7. The VEGF antagonist of claim 6, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

8. The VEGF antagonist of claim 7, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

9. The VEGF antagonist of claim 7, 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.

10. The VEGF antagonist of 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.

11. The VEGF antagonist of claim 10, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

12. The VEGF antagonist of claim 11, wherein the intraocular administration is intravitreal administration.

13. The VEGF antagonist of claim 12, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

14. The VEGF antagonist of claim 13, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

15. Use of a VEGF antagonist in the manufacture of a medicament for use in a method of treating an angiogenic eye disorder in a patient, where the treatment 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.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the form for entry into the European phase (EPO as designated or elected Office) as follows:

Submission number	2205275
PCT application number	PCT/US2012/020855
EP application number	12700590.8
Date of receipt	05 July 2013
Receiving Office	European Patent Office, The Hague
Your reference	N400458-EP DXP
Applicant	
Country	
Documents submitted	package-data.xml application-body.xml AMSPECEPO-1.pdf\N400458EP DXP txb amended claims _clean_.pdf (2 p.) CLMS-HWA.pdf\N400458EP DXP txb amended claims _tracked_.pdf (3 p.) ep-euro-pct.xml epf1200.pdf (4 p.) OTHER-1.pdf\N400458EP DXP txb EP Regional Phase - Jun 13.pdf (2 p.)
Submitted by	CN=D. Power 23473,O=J A Kemp & Co.,C=GB
Method of submission	Online
Date and time receipt generated	05 July 2013, 16:00 (CEST)
Message Digest	A3:64:59:F4:54:41:8A:61:49:95:5F:A3:8E:1D:0D:02:22:93:3B:0E

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated

software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 725A-WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2012/020855	International filing date *(day/month/year)* 11 January 2012 (11.01.2012)	Priority date *(day/month/year)* 13 January 2011 (13.01.2011)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant REGENERON PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 16 July 2013 (16.07.2013)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Mineko Mohri e-mail: pt08.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2012/020855	11.01.2012	13.01.2011

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/18 A61P27/00

Applicant
REGENERON PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Rodrigo-Simón, Ana Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2012/020855

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☒ on paper

      ☒ in electronic form

   b. (time)

      ☒ in the international application as filed

      ☒ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II

Priority

1 The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (13.01.2011). It is to be noted that if the priority is not confirmed, D10 (XP002674122) would be relevant for novelty and inventive step of the claimed subject-matter (see point 8).

Re Item V

Reasoned statement under Rule 43bis1(a)(i) with regard to novelty, inventive step or industrial applicability.

2 **Nomenclature remarks (synonyms):** EYLEA, Aflibercept, VEGFR1R2-Fc [Delta]C1 (a), Zaltrap, AVE-0005, BAY-86-5321, NSC-724770, VEG Trap (R1R2), VEGF Trap and VEGF Trap-Eye.

3 **Claims 1-37** relate to the subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

4 **CLARITY, SUPPORT AND SUFFICIENCY OF DISCLOSURE (Arts. 5 and 6 PCT):**

4.1 **Claims 1-37** do not meet the requirements of Art. 6 PCT because attempt to define the therapeutic compound in terms of the result to be achieved "**VEGF antagonist**".

It appears possible to define the subject-matter in more concrete terms, viz. in terms how the effect is to be achieved, i.e. specific substances or compounds which antagonise VEGF, defined in technical terms (i.e. by means of their chemical structure/ aminoacidic sequence).

Claims 1-37 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function, i.e. antagonist VEGF effect, have not been described.

In the absence of such relationship either disclosed in the application as originally filed or which would have been recognised based on information readily available to the skilled person, the skill person would not know how to make and use compounds that lack any structural definition. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds, contrary to the requirements of Art. 5 PCT.

Claims 1-37 lack therefore clarity, support and disclosure, since the skilled person, after reading the description, would not be able to perform the invention over the whole area claimed without undue burden and without needing inventive skill (Arts. 5 and 6 PCT).

The present application does not provide examples of VEGF antagonists other than the compound known as VEGFR1R2-Fc [Delta]C1(a) (P.2, §9).

It seems that these objections would be overcome by defining the VEGF antagonist in the claims as consisting in (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1).

4.2 **Claims 1-5, 8-25 and 28-37** are additionally not in accordance with Art. 6 PCT because the therapeutic indication "**angiogenic eye disorder**" is vague and not clear. The skilled person is not necessarily aware of which diseases fall under this non-generally accepted therapeutic definition.

This objection could be overcome by specifying the angiogenic eye disorders as in claims 6-7 and 26-27, i.e. age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

4.3 **In view of the above objections no complete examination for the subject-matter of claims 1-37 can be carried out. However, for the sake of completeness and for the purpose of this examination only, the following comments on novelty and inventive step are made on these claims.**

5 **The following prior art documents have been taken into consideration:**

D1: US2007190058

D2: US2006172944

D3: US2005163798

D4: WO0075319

D5: US2006058234

D6: US2005260203

D7: XP26732998

D8: XP009158490

D9: XP002674122

D10: XP002674123

D11: XP002674124

D12: XP002674125

D13: XP002674126

D1 describes the treatment of (wet form) age-related macular degeneration in a mammal, comprising the steps of: a) administering to the mammal a number of first individual doses of an VEGF antagonist; and b) administering to the mammal a number of second individual doses of the VEGF antagonist, wherein the second individual doses are administered less frequently than the first individual doses (claim 1). The preferred VEGF antagonist is Ranibizumab (§112). In example 1 (Fig.1), the administration regime of the VEGF antagonist is every month (Day 0, Month 1 and 2) followed by seven doses every 3 months (P.12,§111).

D2 describes the use of VEGFR1R2-Fc [Delta]C1(a) for the treatment of eye injuries by reducing angiogenesis (§8,17 and claims1-2). The examples show the effect on sutured mice (i.e injury) but not on angiogenic eye disorders.

D3 describes that the fusion protein of SEQ.12 (claim 65; VEGFR1R2-Fc [Delta]C1(a) is useful in the treatment of eye disorders as age macular degeneration and diabetic retinopathy (§122). These uses are however the selection of two lists (compounds and diseases).

D4 describes chimeric polypeptides such as VEGFR1R2-Fc [Delta]C1(a) (P. 87, L.14-88) which are meant to inhibit vascular permeability for attenuation of edema above others (P.14, L7-12).

D5 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.7-8; §67) for the treatment of age related macular degeneration and diabetic retinopathy (claim 23). These conditions are known to be improved by inhibition or reduction of VEGF, which induce undesirable plasma leakage, vascular permeability or undesirable blood vessel growth (P.2, §15).

D6 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.6; claim 4) for the treatment of age related macular degeneration or diabetic retinopathy (claim 5). In D6, the examples show that VEGFR1R2-Fc [Delta]C1(a) has anti-angiogenic properties in induced ischemic retinopathy (P.7, Ex.8) and suppressed 70% of choroidal neovascularization when injected 2, 5, 8, and 11 days after laser treatment (animal model of AMD through laser disruption of Brunch's membrane) (P.8, Ex.9). Additionally, VEGFR1R2-Fc [Delta]C1(a) reduced the pathologic breakdown of the blood retinal barrier (P.8, Ex.11) and the infiltration of neutrophils and macrophages into the damaged cornea (P.9, Ex.2).

D7 (phase I; study with 21 patients), describes the improvement of best corrected visual acuity and the decrease of excess foveal thickness in patients with neovascular age-related macular degeneration patients treated with a single intravitreal injection of VEGF Trap-Eye (2-4mg).

D8 (preliminary study with 6 patients) describes that a single intravitreal injection of VEGF Trap-Eye (2mg) was well tolerated in patients with neovascular age-related macular degeneration (Abstract). The authors conclude that additional testing is to be performed by repeated injections at an interval of 6 weeks or longer (P.149, §2).

D9 describes the use of VEGF-tap-eye for the treatment of diabetic retinopathy (P.147, §4).

D10 (see point 7)

D11 (T-doc) reviews the known VEGF inhibitors used in ophthalmology.

D12 describes the recommended Lucentis® (Ranibizumab) dose 0.5mg to be administered by intravitreal injection once a month in the treatment of (wet) age-related macular degeneration.

D13 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule.

The phase III VEGF Trap-Eye trial methodology is described in D13 but no results are provided in this document. For this reason, the cited passage of D13 cannot be considered as an enabling disclosure of the presently claimed subject-matter. It is furthermore to be noted that the results of this phase III trial are indeed part of the experimental evidence provided in the present application (i.e. example 4 of the present application).

6 **NOVELTY (Arts. 33(1) and (2) PCT):**

Notwithstanding the above objections, the **subject-matter of claims 1-37 is novel** in the sense of Arts. 33(1) and (2) PCT because the specific administration regime of the claimed compounds has not been found to be disclosed in the prior art at hand.

7 **INVENTIVE STEP (Arts. 33(1) and (3) PCT):**

Notwithstanding the above objections, the subject-matter of **claims 1-37 is not inventive** because:

7.1 **The closest prior art, D13** (phase II study summary), describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by 40 additional weeks treatment on a PNR (as needed) dosing schedule.

7.2 **The difference** with D13 lies in that the present application provides the following:

7.2.1 **Compound** (i.e.VEGF antagonist):

(a) 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 (claims 8 and 28)

(b) VEGF antagonist is a VEGF receptor-based chimeric molecule (claims 9 and 29), a VEGF receptor-based chimeric molecule which comprises VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID N0:1 (claims 10 and 30) or a - 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 1D NO:2; and (3) a multimerization component comprising aminoacids 232-457 of SEQ.ID.2 (claims 11 and 31)

(c) the VEGF antagonist being VEGFR1R2-Fc [Delta]C1(a) (P.2, §9)

Administration regime of the above compounds:

- a single initial dose of, followed by one or more secondary doses, followed by one or more tertiary doses; 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

7.3 **The problem to be solved** lies in the provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.

7.4 **There are different solutions** provided by the claims which are directed to the administration of compounds (a)-(c) in a single initial dose, followed by one or more secondary doses, followed by one or more tertiary doses; 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; wherein:

a) 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 (claims 8 and 28) **(Solution 1)**

(b) VEGF antagonist is a VEGF receptor-based chimeric molecule (claims 9 and 29), a VEGF receptor-based chimeric molecule which comprises VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID N0:1 (claims 10 and 30) or a - 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 1D NO:2; and (3) a multimerization component comprising aminoacids 232-457 of SEQ.ID.2 (claims 11 and 31) **(Solution 2)**

(c) the VEGF antagonist being VEGFR1R2-Fc [Delta]C1(a) (SEQ.1)(P.2, §9) **(Solution 3)**

7.5 **In support of an inventive step** the applicant has provided the following examples:

Ex.1: a single intravitreal injection of VEGFT in neovascular AMD subjects resulted in reduction of pathological retinal thickness.

Ex.2: intravitreal injection of VEGFT every 4 or 12 weeks in neovascular AMD subjects resulted in increase of visual acuity.

Ex.3: four injections of VEGFT over an 8-week period resulted in improved visual acuity.

Ex.5: patients with diabetic macular edema which were eligible for laser treatments showed gain in visual acuity when treated with VEGFT (Table 2).

Ex.6: naive patients with macular edema secondary to central retinal vein occlusion treated with 6 monthly intravitreal VEGFT injections showed improvement of visual acuity at week 24 which was maintained through week 52.

7.5.1 The most relevant example for the claimed subject-matter seems to be **Ex.4** where VEGFT demonstrated non-inferiority of efficacy compared to Ranibizumab.

In this example, VEGFT was administered every 4 weeks (1Q4 and 0,5Q4) or every 4 weeks to week 8 with additional administrations every 8 weeks (2Q8) (Fig.1). The effects after 52 weeks treatment are summarised in Table 1 where it is shown that the claimed administration protocol achieved similar effect than 0,5mg Ranibizumab monthly administered (non-inferiority statistical analysis).

It is to be noted that the applicant refers in the examples to the used compound as "VEGFT". However, in P.2, §9 is indicated that, the VEGFT is VEGFR1R2-Fc [Delta]C1(a) (i.e.VEGF Trap-Eye). It is therefore to be considered that the "VEGFT" meant in the present examples is indeed VEGFR1R2-Fc [Delta]C1(a). Additionally, in D7, which is the scientific publication of the results of the present Ex.1, the used compound is VEGFR1R2-Fc [Delta]C1(a).

In summary, the above results can only be attributed to the specific VEG antagonist being (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1).

7.5.2 **Generalisation to the disclosed angiogenic eye disorders:**

It is to be noted that the technical effect shown is limited to macular degeneration. The generalisation to the treatment of diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization is however possible because these eye disorders have in common a process of pathogenic angiogenesis which is plausibly expected to be successfully treated with the provided VEGFR1R2-Fc [Delta]C1(a) protocol.

7.5.3 **Generalisation to any VEGF antagonist not possible:**

This effect cannot be generalised to any compound which could fall under the functional definition "VEGF antagonist" in general or under the VEGF antagonist as defined in (a)-(c) (see point 7.2 above). This generalisation is not possible because each antagonist (as above defined) has different nature (i.e. tridimensional structure, half life, binding affinity, etc.) and therefore different antagonistic effect. In summary, the above VEGF antagonists are not necessarily expected to achieve the effect shown for VEGFR1R2-Fc [Delta]C1 (a) (SEQ.1) when administered as claimed.

The technical effect of any VEGF antagonist in general or as defined in (a)-(c) (i.e. Solutions 1-2), cannot be acknowledged.

A technical effect solving a technical problem has to be achieved by all embodiments falling within the scope of the claims. Claims covering embodiments not achieving such effect, not shown to have achieved such effect are considered not to solve the underlying technical problem. These claims are therefore not inventive.

7.6 Starting from the closest prior art, D13, **any VEGF antagonist as defined in a-c (i.e. Solutions 1-2)** administered in a single initial, followed by one or more secondary doses, followed by one or more tertiary doses; 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 **are obvious non-inventive solutions** for use in the treatment of age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization because their technical effect has not been demonstrated (i.e. the problem has not been shown to be solved over the whole scope).

7.7 **Claims 1-37 are not in accordance with the requirements of Arts. 33(1) and (3) PCT.**

7.8 The attention of the applicant is drawn to the fact that the technical effect of the claimed protocol, wherein the VEG antagonist is VEGFR1R2-Fc [Delta]C1 (a) (SEQ.1) has been demonstrated in the present application (Solution 3).

Starting from the closest prior art, D13, the VEGF antagonist consisting in/ being **VEGFR1R2-Fc [Delta]C1(a)** (SEQ.1) administered in a single initial, followed by one or more secondary doses, followed by one or more tertiary

doses; 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 is a **non-obvious and inventive solution** for use in the treatment of age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization becuase its technical effect has been demonstrated (i.e. plausibly solving the problem over the whole scope). The skilled person would have not come to this solution without inventive skill.

Re Item VI

Certain documents cited

8 **D10** (XP002674122) describes the results of the present example 5. The administration schedule in Fig.1 "2mg q8 wks" is the same than in the present claims.

This document could become relevant for the assessment of novelty and inventive step if the priority date 13.01.2011 is not confirmed.

Re Item VIII

9 **Certain observations on the international application Clarity (Art.6 PCT):**

See point 4.

10 **AMENDMENTS**

10.1 The attention of the applicant is drawn to the fact that, notwithstanding the above comments to the partial subject-matter of this application which could be regarded as being in accordance **with Arts.5, 6 and 33(1) and (3) PCT, it is the applicant's sole responsibility to amend the application documents in accordance with Art.34 or Art.19 PCT.**

10.2 **When /if carrying amendments**, and in order to facilitate the examination of the conformity of the amended application with the requirements of Article 34 (2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate precisely the passages of the application as filed on which these amendments are based (also Rule 66.8 (a) PCT).

Only amendments with a clearly identified basis on the application as originally filed will be taken into account for the international preliminary examination report.

10.3 **If this application enters in the regional phase**, it is to be noted that claims referred to methods of treatment are not patentable pursuant to Art.53(c) EPC. The allowable wording for further medical use claims according to the EPC2000 is the following:

Independent claim: "Compound x for use in the treatment of disease y"

Dependent claims: "Compound x for use according to claim a, wherein..."

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Date
19.08.13

Reference	Application No./Patent No.
	12700590.8 - 1456

Applicant/Proprietor
Regeneron Pharmaceuticals, Inc.

Notification of the data mentioned in Rule 19(3) EPC

In the above-identified patent application you are designated as inventor/co-inventor.
Pursuant to Rule 19(3) EPC the following data are notified herewith:

DATE OF FILING	: 11.01.12
PRIORITY	: US/13.01.11/ USP201161432245 : US/21.01.11/ USP201161434836 : US/21.11.11/ USP201161561957
TITLE	: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
DESIGNATED STATES	: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Receiving Section

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EPO Form 1204 12.07

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Date
21.08.13

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1456
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Communication pursuant to Rules 161(1) and 162 EPC

1. Comments on the written opinion and amendment of the application (R. 161(1) EPC)

The above-mentioned international (Euro-PCT) application has entered the European phase.

The EPO as International Searching Authority and, where a demand under Article 31 PCT was filed, also as International Preliminary Examining Authority has drawn up a written opinion on this application or the EPO as Supplementary International Searching Authority has issued explanations pursuant to Rule 45*bis*.7(e) PCT to the supplementary international search report.

In accordance with Rule 161(1) EPC, you may comment on the written opinion or on the explanations to the supplementary international search report within a **non-extendable period of six months** after notification of the present communication.

Under Articles 28, 41 PCT and Rules 52, 78 PCT the application may be amended before a designated or elected Office, and in accordance with Rule 137(2) EPC the applicant may amend the description, claims and drawings of his own volition together with any comments, corrections or amendments made in response to the communication under Rule 161(1) EPC.

Whether or not you have already done so, you now have a further opportunity to file amended claims or other application documents within the above-mentioned period.

Please note that under Rule 137(2) and (3) EPC as in force from 1 April 2010, you may amend the description, claims and drawings of your own volition in response to this communication, if the international search report has been drawn up on or after 1 April 2010 or the EPO has issued a supplementary international search report. In these cases no further amendments may be made without the consent of the Examining Division. This may be in particular relevant if you have already filed comments/amendments with respect to a written opinion of the International Searching Authority or an international preliminary examination report, or to any explanations pursuant to Rule 45*bis*.7(e) PCT to the supplementary international search report, which however do not address the deficiencies noted therein and you choose not to react to the present communication.

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

The claims applicable on expiry of this period, i.e. those filed on entry into the European phase or in response to the present communication, will form the basis for the calculation of any claims fee to be paid (see p. 2).

Registered letter
EPO Form 1226BB 04.12 (NFS) EUCL (12/08/13)

2. Claims fees under Rule 162 EPC

If the application documents on which the European grant procedure is to be based comprise more than fifteen claims, a claims fee shall be payable for the sixteenth and each subsequent claim within the period provided for in Rule 159(1) EPC.

☑ Based on the application documents currently on file, all necessary claims fees have already been paid (or the documents do not comprise more than 15 claims).

☐ All necessary fees will be/have been debited automatically according to the automatic debit order.

☐ The claims fees due for the claims ..... to ..... were not paid within the above-mentioned period.

Any outstanding claims fee, either based on the current set of claims or on any amended claims to be filed pursuant to Rule 161 EPC (see page 1), may still be validly paid within a **non-extendable period of six months** after notification of this communication (R. 162(2) EPC).

If a payment is made for only some of the claims, you must indicate for which claims it is intended. If a claims fee is not paid in due time, the claim concerned is deemed to be abandoned (R. 162(4) EPC).

If claims fees have already been paid, but on expiry of the above-mentioned period there is a new set of claims containing fewer fee-incurring claims than before, the claims fees in excess of those due under Rule 162(2), second sentence EPC will be refunded (R. 162(3) EPC).

The claims fee is currently

EUR 225 for the 16th and each subsequent claim up to the limit of 50
EUR 555 for the 51st and each subsequent claim

Note to users of the automatic debiting procedure
Unless the EPO receives prior instructions to the contrary, the fees for all claims incurring fees will be debited on the last day of the period for payment. For further details see the Arrangements for the automatic debiting procedure, Supplement to OJ EPO 3/2009.

Important information concerning fee amounts
Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment.** The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (**www.epo.org**) and can be found under **www.epo.org/schedule-of-fees**, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

For the Examining Division

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Date
23.10.13

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1456 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Communication of European publication number and information on the application of Article 67(3) EPC

The provisional protection under Article 67(1) and (2) EPC in the individual Contracting States becomes effective only when the conditions referred to in Article 67(3) EPC have been fulfilled (for further details, see information brochure of the European Patent Office "National Law relating to the EPC" and additional information in the Official Journal of the European Patent Office).

Pursuant to Article 153(3) EPC the publication under Article 21 PCT of an international application for which the European Patent Office is a designated or elected Office takes the place of the publication of a European patent application.

The bibliographic data of the above-mentioned Euro-PCT application will be published on 20.11.13 in Section I.1 of the European Patent Bulletin. The European publication number is 2663325.

In all future communications to the European Patent Office, please quote the application number plus Directorate number.

For the Examining Division

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Application No.	Ref.	Date
12 700 590.8 - 1456	N400458-EP DXP	21.08.2014
Applicant Regeneron Pharmaceuticals, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter
EPO Form 2001 12.10CSX

Rodrigo-Simón, Ana
Primary Examiner
For the Examining Division

Enclosure(s): 9 page/s reasons (Form 2906)

Registered letter
EPO Form 2001 12.10CSX

1 The examination is being carried out on the **following application documents**

Description, Pages

1-18 as published

Sequence listings, SEQ ID NO

1, 2 as published

Claims, Numbers

1-15 filed on 05-07-2013

Drawings, Sheets

1/1 as published

2 New claims filed on 05.07.2013 are in accordance with the requirements of Art. 123(2) EPC because their subject-matter does not go beyond the application as originally filed.

3 Claims 1-15 enjoy priority rights from the filing date of the priority document (13.01.2011). D10 (XP002674123), cited in the ISR, is therefore not prior art in the sense of Art. 54(2) EPC.

4 **CLARITY, SUPPORT AND SUFFICIENCY OF DISCLOSURE (Arts. 83 and 84 EPC):**

4.1 **Claims 1-15** do not meet the requirements of Art. 84 EPC because **claims 1-9 and 15** attempt to define the therapeutic compound in terms of the result to be achieved "**VEGF antagonist**".

It appears possible to define the subject-matter in more concrete terms, viz. in terms how the effect is to be achieved, i.e. specific substances or compounds which antagonise VEGF, defined in technical terms (i.e. by means of their chemical structure/ aminoacidic sequence).

Claims 1-15 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function, i.e. antagonist VEGF effect, have not been described.

In the absence of such relationship either disclosed in the application as originally filed or which would have been recognised based on information readily available to the skilled person, the skill person would not know how to make and use compounds that lack any structural definition. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds, contrary to the requirements of Art. 83 EPC.

Claims 1-15 lack therefore clarity, support and disclosure, since the skilled person, after reading the description, would not be able to perform the invention over the whole area claimed without undue burden and without needing inventive skill (Arts. 83 and 84 EPC).

The present application does not provide examples of VEGF antagonists other than the compound known as VEGFR1R2-Fc [Delta]C1(a) (P.2, §9).

It seems that these objections would be overcome by defining the VEGF antagonist in the claims as consisting in (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1).

4.2 **Claims1-3 and 6-15** are additionally not in accordance with Art. 84 EPC because the therapeutic indication "**angiogenic eye disorder**" is vague and not clear. The skilled person is not necessarily aware of which diseases fall under this non-generally accepted therapeutic definition.

This objection could be overcome by specifying the angiogenic eye disorders as in claims 4-5, i.e. age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

4.3 Medical use **claims 2-15** are additionally not in accordance with the requirements of Art. 84 EPC because:

Dependent medical use **claims 2-14** should be drafted: "compound x <u>for use according to</u> claim z, wherein [...] ".

Claim 15 is a combination of the Swiss type format and the new format according to the EPC 2000. The attention of the applicant is drawn to the fact that the Swiss type format is: "Use of compound x in the manufacture of a medicament for treating disease z".

4.4 **In view of the above objections (Arts. 83 and 84 EPC) no complete examination for the subject-matter of claims 1-15 can be carried out. However, for the sake of completeness and for the purpose of this communication, the following comments are made on the subject-matter of the present application.**

5 It is to be noted that the following terms are synonyms: EYLEA, Aflibercept, VEGFR1R2-Fc[Delta]C1 (a), Zaltrap, AVE-0005, BAY-86-5321, NSC-724770, VEG Trap(R1R2), VEGF Trap and VEGF Trap-Eye.

6 **The following prior art documents have been taken into consideration:**

D1: US2007190058

D2: US2006172944

D3: US2005163798

D4: WO0075319

D5: US2006058234

D6: US2005260203

D7: XP26732998

D8: XP009158490

D9: XP002674122

D11: XP002674124

D12: XP002674125

D13: XP002674126

D1 describes the treatment of (wet form) age-related macular degeneration in a mammal, comprising the steps of: a) administering to the mammal a number of first individual doses of an VEGF antagonist; and b) administering to the mammal a number of second individual doses of the VEGF antagonist, wherein the second individual doses are administered less frequently than the first individual doses (claim 1). The preferred VEGF antagonist is Ranibizumab (§112). In example 1 (Fig.1), the administration regime of the VEGF antagonist is every month (Day 0, Month 1 and 2) followed by seven doses every 3 months (P.12,§111).

D2 describes the use of VEGFR1R2-Fc [Delta]C1(a) for the treatment of eye injuries by reducing angiogenesis (§8,17 and claims1-2). The examples show the effect on sutured mice (i.e injury) but not on angiogenic eye disorders.

D3 describes that the fusion protein of SEQ.12 (claim 65; VEGFR1R2-Fc [Delta]C1(a) is useful in the treatment of eye disorders as age macular degeneration and diabetic retinopathy (§122). These uses are however the selection of two lists (compounds and diseases).

D4 describes chimeric polypeptides such as VEGFR1R2-Fc [Delta]C1(a) (P. 87, L.14-88) which are meant to inhibit vascular permeability for attenuation of edema above others (P.14, L7-12).

D5 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.7-8; §67) for the treatment of age related macular degeneration and diabetic retinopathy (claim 23). These conditions are known to be improved by inhibition or reduction of VEGF, which induce undesirable plasma leakage, vascular permeability or undesirable blood vessel growth (P.2, §15).

D6 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.6; claim 4) for the treatment of age related macular degeneration or diabetic retinopathy (claim 5). In D6, the examples show that VEGFR1R2-Fc [Delta]C1(a) has anti-angiogenic properties in induced ischemic retinopathy (P.7, Ex.8) and suppressed 70% of choroidal neovascularization when injected 2, 5, 8, and 11 days after laser treatment (animal model of AMD through laser disruption of Brunch's membrane) (P.8, Ex.9). Additionally, VEGFR1R2-Fc [Delta]C1(a) reduced the pathologic breakdown of the blood retinal barrier (P.8, Ex.11) and the infiltration of neutrophils and macrophages into the damaged cornea (P.9, Ex.2).

D7 (phase I; study with 21 patients), describes the improvement of best corrected visual acuity and the decrease of excess foveal thickness in patients with neovascular age-related macular degeneration patients treated with a single intravitreal injection of VEGF Trap-Eye (2-4mg).

D8 (preliminary study with 6 patients) describes that a single intravitreal injection of VEGF Trap-Eye (2mg) was well tolerated in patients with neovascular age-related macular degeneration (Abstract). The authors conclude that additional testing is to be performed by repeated injections at an interval of 6 weeks or longer (P.149, §2).

D9 describes the use of VEGF-tap-eye for the treatment of diabetic retinopathy (P.147, §4).

D11 (T-doc) reviews the known VEGF inhibitors used in ophthalmology.

D12 describes the recommended Lucentis® (Ranibizumab) dose 0.5mg to be administered by intravitreal injection once a month in the treatment of (wet) age-related macular degeneration.

D13 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule.

The phase III VEGF Trap-Eye trial methodology is described in D13 but no results are provided in this document. For this reason, the cited passage of D13 cannot be considered as an enabling disclosure of the presently claimed subject-matter. It is furthermore to be noted that the results of this phase III trial are indeed part of the experimental evidence provided in the present application (i.e. example 4 of the present application).

7 **Notwithstanding the above objections (Arts. 83 and 84 EPC), it is to be noted that the subject-matter of claims 1-15 is additionally not inventive in the sense of Art. 56 EPC because:**

7.1 **The closest prior art, D13** (phase II study summary), describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by 40 additional weeks treatment on a PNR (as needed) dosing schedule.

7.2 **The difference** with D13 lies in that the present application proposes the use of:

Compound (i.e.VEGF antagonist):

(a) 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

(b) VEGF antagonist is a VEGF receptor-based chimeric molecule (claims 9 and 29), a VEGF receptor-based chimeric molecule which comprises VEGFR1R2-FcAC1(a) encoded by the nucleic acid sequence of SEQ ID N0:1 (claims 10 and 30) or a - 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 1D NO:2; and (3) a multimerization component comprising aminoacids 232-457 of SEQ.ID.2

(c) VEGF antagonist is VEGFR1R2-Fc [Delta]C1(a) (P.2, §9)

Administration regime of the above compounds:

- a single initial dose of, followed by one or more secondary doses, followed by one or more tertiary doses; 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

7.3 **In support of an inventive step** the applicant has provided the following examples:

Ex.1: a single intravitreal injection of VEGFT in neovascular AMD subjects resulted in reduction of pathological retinal thickness.

Ex.2: intravitreal injection of VEGFT every 4 or 12 weeks in neovascular AMD subjects resulted in increase of visual acuity.

Ex.3: four injections of VEGFT over an 8-week period resulted in improved visual acuity.

Ex.5: patients with diabetic macular edema which were eligible for laser treatments showed gain in visual acuity when treated with VEGFT (Table 2).

Ex.6: naive patients with macular edema secondary to central retinal vein occlusion treated with 6 monthly intravitreal VEGFT injections showed improvement of visual acuity at week 24 which was maintained through week 52.

7.3.1 The most relevant example for the claimed subject-matter seems to be **Ex.4** where VEGFT demonstrated non-inferiority of efficacy compared to Ranibizumab.

In this example, VEGFT was administered every 4 weeks (1Q4 and 0,5Q4) or every 4 weeks to week 8 with additional administrations every 8 weeks (2Q8) (Fig.1). The effects after 52 weeks treatment are summarised in Table 1 where it is shown that the claimed administration protocol achieved similar effect than 0,5mg Ranibizumab monthly administered (non-inferiority statistical analysis).

It is to be noted that the applicant refers in the examples to the used compound as "VEGFT". However, in P.2, §9 is indicated that, the VEGFT is VEGFR1R2-Fc [Delta]C1(a) (i.e.VEGF Trap-Eye). It is therefore to be considered that the "VEGFT" meant in the present examples is indeed VEGFR1R2-Fc [Delta]C1(a). Additionally, in D7, which is the scientific publication of the results of the present Ex.1, the used compound is VEGFR1R2-Fc [Delta]C1(a).

In summary, the above results can only be attributed to the specific VEG antagonist being (and not comprising) VEGFR1R2-Fc [Delta]C1(a) (SEQ.1) (P.2, §9).

7.3.2 **Generalisation to any VEGF antagonist not possible:**

This effect cannot be generalised to any compound which could fall under the functional definition "VEGF antagonist" in general or under the VEGF antagonist as defined in (a)-(b). This generalisation is not possible because each antagonist (as above defined) has different nature (i.e. tridimensional structure, half life, binding affinity, etc.) and therefore different antagonistic effect. In summary, the above VEGF antagonists are not necessarily expected to achieve the effect shown for VEGFR1R2-Fc [Delta]C1(a) (SEQ.1) when administered as claimed.

A technical effect for any VEGF antagonist in general or as defined in (a)-(b) cannot be acknowledged.

7.3.3 **Administration regime as claimed not shown:**

The claims are directed to several administrations protocols. It is however to be noted that in the above examples none of these protocols (neither using any VEGF antagonist optionally as defined (a)-(b) nor taking the specific VEGFR1R2-Fc [Delta]C1(a)) have been demonstrated to achieve a successful treatment of any of the claimed diseases.

A technical effect cannot be acknowledged for any VEGF antagonist optionally defined in a-b or even for VEGFR1R2-Fc [Delta]C1(a) (SEQ.1) administered in a single initial dose, followed by one or more secondary doses, followed by one or more tertiary doses; 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 for use in the treatment of age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.

7.3.4 **In summary, a technical effect for the claimed subject-matter (i.e. dosage regime) cannot be acknowledged**

7.4 **The attention of the applicant is drawn to the fact that according to the Enlarged Board of Appeal decision G2/08:**

- Where it is already known to use a medicament to treat an illness, Article 54 (5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness.

- Such patenting is also not excluded where a **dosage regime** is the only feature claimed which is not comprised in the state of the art.

- Furthermore, if the distinguishing feature of a claim seeking patent protection for a known medicament to be used for a different treatment of the same illness is a dosage regime and is something else than a mere selection from a prior broader disclosure, **a new technical effect caused by said feature shall be considered when examining inventive step under Article 56 EPC**.

7.5 A technical effect solving a technical problem has to be achieved by all embodiments falling within the scope of the claims. Claims covering embodiments not achieving such effect, not shown to have achieved such effect, and thus not solving the underlying technical problem, do not meet the requirements of Art. 56 EPC.

7.6 **The problem to be solved** *"provision of improved protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* has not been shown to be solved by the claimed solutions in the present application. The objective technical problem needs to be reformulated to the less ambitious one *"provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* for which the claimed solutions are obvious in view of D13.

7.7 It is furthermore to be noted that the same problem solution approach would apply taking D1, D12 or D8 as closest prior art.

7.8 **The subject-matter of claims 1-15 is not in accordance with the requirements of Arts. 56 EPC.**

8 **The attention of the applicant is drawn to the fact that if the deficiencies above mentioned are not rectified, refusal of the application under Art.97 (2) EPC is to be expected in the next step of the procedure.**

9 **AMENDMENTS**

Care should be taken during revision not to add subject-matter which extends beyond the content of the application as originally filed (Art. 123 (2) EPC).

In order to facilitate the examination of the conformity of the amended application with the requirements of Art. 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate precisely the passages of the application as filed on which these amendments, notably new combinations of features, are based (cf. Guidelines H; CI and CII-2.2).

Documents making up the patent application and those replacing them must comply with the requirements of Rule 49 EPC.

J A • K E M P

BY ONLINE FILING

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17 December 2014

Dear Sirs

European Patent Application No. 12700590.8 -1456
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP DXP

In response to the Communication of 21 August 2014, please amend the application by replacing the claims at present on file with the attached retyped claims.

In order to assist the Examiner in assessing the amendments being made, a copy of the previous claims is also attached, which shows the changes tracked-in.

Summary

The claims are amended to specify the type of disease which can be treated which disorders involve a vascular leakage into the eye. The claims are now specific to a VEGF antagonist defined by a sequence listing and as such provides a result which offers an improved dosing regime to patient suffering from these conditions. The regime makes it possible to reduce the frequency of dosing and reduce the amount of drug needed thereby decreasing side effects due to the drug and reducing the frequency of administration.

Amendments & Basis

Whilst not necessarily agreeing with the objections raised, in order to facilitate prosecution a number of amendments have been made to the claims.

Claim 1 has been amended to:

- specify two or more secondary doses are administered, with reference to two secondary doses finding basis in original claim 3;

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- replace the previous ranges for the time intervals between doses with instead reference to 4 weeks for the secondary doses and 8 weeks for the tertiary doses, which finds basis both in endpoints of the ranges specified in original claim 1, as well as in original claims 3 and 4;

- specify that the angiogenic eye disorder is one of those listed in previous claim 4 which finds basis, for instance, in claim 6 of the application as filed; and

- define the VEGF antagonist as one comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1, with that amendment finding basis, for instance, in original claim 9.

New claims 2 to 6 have been added which are dependent claims, each referring to one of the conditions now listed by claim 1, with again basis being provided by original claim 6.

Claim 7, corresponding to previous claim 9 has been amended to reflect the wording of claim 1.

Previous claims 2 to 4 and 15 have been deleted.

It is appreciated that the description may require amendment for conformity with the new claims, but it is requested that such amendment be deferred until after the Examining Division have confirmed that the new claims are allowable.

Clarity, Support & Sufficiency – Articles 83 & 84 EPC – Item 4 of the Report

Overview

In order to facilitate prosecution, claim 1 has been amended to narrow the scope of the claims in three significant ways:

- the VEGF antagonist is now specifically defined as comprising the VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

- the angiogenic eye disorder which can be treated has been limited to a narrow group of disorders, comprising five named disorders; and

- at least two secondary doses are now required and the interval between doses for both the secondary doses and the tertiary doses has been much more narrowly defined.

All three of those amendments further focus the claims towards what is dealt with in the specific Examples within the specification, particularly Example 4 which the Examiner has flagged up as the most relevant Example. The Applicant is prepared to compromise and the amendments are made in that spirit, though to have to narrow the claims any further would unfairly penalise the Applicant and fail to recognise the contribution made.

The Applicant should not have to limit the claims to exactly what is presented in the Examples as the Examples act as a guide which allow the skilled person to carry out

the invention across the full scope of the amended claims without undue experimentation. The claims are based on reasonable generalisation of what is exemplified.

Given the substantial narrowing of the claims in order to facilitate prosecution, it is believed that the Division will be able to acknowledge compliance with Articles 83 & 84 EPC.

Item 4.1

Claim 1 has been amended to define the VEGF antagonist by reference to the antagonist encoded by the specific nucleotide sequence of SEQ ID No: 1. The claim therefore no longer covers the use of any VEGF antagonist and instead has been tightly focussed on the use of a particular antagonist, which is that used in the Examples of the present application.

The comments made in the final paragraph of Item 4.1 are noted. However, having to amend to "*consisting of*", rather than "*comprising*", claim language would be highly restrictive, fail to recognise the contribution made and prevent the claims from providing meaningful protection. Some generalisation should be allowed, particularly given that the skilled person would be readily able to tell whether a particular VEGF antagonist comprising the amino acid sequence encoded by SEQ ID NO:1 was active and so would be able to put what is claimed into practice.

Claim 1 requires both that the VEGF antagonist be functional and that it is encoded by the specific nucleotide sequence of SEQ ID NO:1. If claim 1 had to be amended to "*consisting of*" claim language, then third parties could attempt to design around the claim by making simple modifications to the nucleic acid sequence of SEQ ID NO:1, such as modifying the coding sequence to give an antagonist comprising a few amino acids at the termini of the protein, whilst still taking full advantage of the dosage regimen provided by the application as filed.

Amended claim 1 therefore complies with Articles 83 & 84 EPC in relation to the VEGF antagonist and should not have to be limited further.

Item 4.2

Again, purely in order to facilitate prosecution, claim 1 has been amended to limit it to the specific, named disorders specified by previous claim 4. Given that the amendment proposed by the Examining Division has been made, it is believed that the Division will be able to acknowledge that the definition of the disease state to be treated is clear.

Item 4.3

Dependent claims 2 to 11 are all now in the Article 54(5) EPC approved format.

Previous claim 15 has been deleted rendering the objection raised in respect of that claim moot.

Inventive Step - Items 6 and 7 of the Examination Report

(a) The technical effect is achieved across the breadth of the claims

It is believed that the amendments made to claim 1 will also help to address the objections raised in Item, 7.

Item 7.3.1 of the Report indicates the data presented in Example 4 of the present application is the most relevant and the amendments made to claim 1 therefore focus claim 1 tightly around what is presented in that Example to help facilitate prosecution.

More specifically, amended claim 1 is tightly focussed around what is demonstrated in Example 4, as amended claim 1:

(i) refers to employing a VEGF antagonist comprising the antagonist encoded by the nucleotide encoded by SEQ ID NO: 1, which corresponds to that used in Example 4 (the Example refers to VEGFT simply as an abbreviation for "VEGF-trap", which is what VEGFR1R2-FcΔC1(a) represents because it "traps" VEGF);

(ii) refers to a dosing regimen encompassing that given to the 2Q8 group in Example 4 of an initial dose, then two secondary doses at four week intervals, and then tertiary doses given at 8 week intervals; and

(iii) refers to a narrow group of five specific, named angiogenic eye disorders, that includes AMD dealt with in Example 4, as well as four other similar conditions where the mechanism of action of the antagonist seen for AMD would also be expected to work for those additional conditions allowing them to also be successfully treated.

Hence, for the equivalent reasons set out above for Articles 83 & 84 EPC, what is claimed also solves the technical problem across the breadth of the claims, and is now tightly based around what is exemplified.

The Applicant has more than met the Examiner half-way. To have to narrow the claims even further and use "*consisting of*" language in respect of the definition of the antagonist would unfairly penalise the Applicant. The skilled person would be able to readily determine if other VEGF antagonists comprising VEGFR1R2-FcΔC1(a) encoded by SEQ ID NO: 1 would work and claim 1 does require functionality. The Applicant is not seeking to cover homologs with low sequence identity and the like, the claims are based on reasonable generalisation and require that the at least the amino acid sequence encoded by SEQ ID NO:1 be present and be able to act as a VEGF antagonist.

In respect of the disease to be treated, again claim 1 has been narrowed substantially to tightly base it around the AMD condition dealt with in Example 4, so the claim refers to AMD and four other similar eye disorders. All of the disorders specified involve vascular leakage into the eye which the VEGF antagonist targets and so the narrow list of conditions specified by claim 1 is reasonable.

As such, what is claimed will display the same technical effect as is demonstrated in Example 4 across the full breadth of the claims. The technical effect for the regimen can therefore be taken into account for the reasons acknowledged in G2/08.

(b) Inventive step over the prior art

The Report adopts D13 as the closest prior art. As acknowledged in Item 6, in the summary given at page 5 of the Examination Report, D13 does not provide any experimental results:

> "*The phase III VEGF Trap-Eye trial methodology is described in D13 but no results are provided in this document. For this reason, the cited passage of D13 cannot be considered an enabling disclosure of the presently claimed subject-matter*"

Further, whilst D13 refers to particular dosages, it makes no reference to the regimen now specified by claim 1 which is that given in Example 4 of the present application, to the 2Q8 group.

The 2Q8 group in Example were given an initial dose of the antagonist, then two secondary doses at four week intervals and then further tertiary doses at eight week intervals, with Example 4 showing such a regimen gives as good a result as ranibizumab. That regimen is reflected in claim 1.

The technical problem to be solved may be formulated as the provision of a new regimen for effectively treating the conditions specified by claim 1.

The solution to that technical problem is provided by the regimen of claim 1. That solution would not have been obvious from D13. As discussed above, D13 does not present any actual experimental results and so the skilled person would not know what regimen of those referred to in D13 would be effective. The regimen specified by claim 1 strikes the balance between efficacy and using less frequent dosing than the monthly dosing of other groups which will have the advantages of helping reduce the amount of drug needed and also potentially decrease side-effects due to the drug being administered less frequently.

D13 includes no hint of that. The reason D13 assesses several regimens is that it does not know which of the regimens will best strike that balance. The skilled person would therefore not have arrived at what is claimed for the reasons effectively acknowledged in the Examination Report, namely that D13 does not provide an enabling disclosure.

The Examination Report also cites D1, D8 and D12, yet none of those documents rectifies the deficiencies of D13. In more detail:

- D8 describes a Phase I trial of VEGF-trap where subjects were given a single dose of the VEGF antagonist and then studied for safety, tolerability and bioactivity (see Abstract). Such a phase I trial involving a single dose would tell the skilled person nothing about what dosing regimen to apply.

- D1 and D12 are both concerned with ranizumab/lucentis®, which is an antibody based antagonist, rather than the VEGF-trap that the claims are based around. Given the extensive comments made in the Examination Report regarding extrapolating results from one type of antagonist to another, it is believed that the Division will be able to acknowledge that D1 and D12 would not have given the skilled person any pointer to the technical solution due to the document being concerned with a different type of antagonist. Further D12, which provides prescribing information for ranizumab/lucentis® directs to apply monthly dosing, not the regimen specified by claim 1 and so is not just concerned with a different drug, but a different regimen as well.

Overall, the skilled person would therefore not have arrived at what is claimed from any of the cited prior art documents, whether considered individually or in combination with each other. The subject matter of the amended claims is inventive.

Other Points - Item 8 of the Examination Report

The comments made are noted. It is believed the substantial amendments made to the claims to facilitate prosecution though will mean the Examining Division are able to acknowledge that the new claims are allowable.

Conclusions

If any residual points remain outstanding, the Examiner is welcome to telephone the undersigned. Purely as a precaution, the previous request for Oral Proceedings is maintained in the event that the Examining Division contemplate refusal of the present application at any time.

Please note that the Applicant does not consent to amendments being made to the claims without their prior consultation. Hence, if the Examiner wishes to propose amendments to the claims, the Examiner is asked to telephone the undersigned.

Yours faithfully

Electronically Signed
DR DAVID POWER

Europäisches Patentamt
European Patent Office
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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	N400458EP

	Description of document	Original file name	Assigned file name
1	Reply to examination report	N400458EP DXP response Dec 14.pdf	EXRE3-1.pdf
2	Amended claims (clean copy)	N400458EP DXP amended claims - clean - Dec 2014.pdf	CLMS-1.pdf
3	Amended claims with annotations	N400458EP DXP amended claims - tracked - Dec 2014.pdf	CLMS-HWA-1.pdf

Signatures

Place:	**London**
Date:	**17 December 2014**
Signed by:	**David Power 23473**
Capacity:	**(Representative)**

CLAIMS

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(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 about 0.5 mg to about 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

CLAIMS – TRACKED

1. 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~~ two 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;

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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

~~2. The VEGF antagonist of claim 1, wherein:~~

~~(a) 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; or~~

~~(b) only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.~~

~~3. The VEGF antagonist of claim 1 or 2, wherein:~~

~~(a) each tertiary dose is administered 8 weeks after the immediately preceding dose; or~~

~~(b) 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.~~

~~4. The VEGF antagonist of any one of the preceding claims, 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.~~

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.

~~6. The VEGF antagonist of any one of the preceding claims, 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.~~

~~7. The VEGF antagonist of claim 6, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.~~

~~8. The VEGF antagonist of claim 7, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.~~

~~9~~7. The VEGF antagonist for use according to ~~of claim 7~~ any one of the preceding claims, wherein the VEGF ~~receptor-based chimeric molecule~~ 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.

~~10~~8. The VEGF antagonist for use according to ~~of~~ 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.

~~11~~9. The VEGF antagonist for use according to ~~of~~ claim ~~10~~8, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

~~12~~10. The VEGF antagonist for use according to ~~of~~ claim ~~11~~9, wherein the intraocular administration is intravitreal administration.

~~13~~11. The VEGF antagonist for use according to ~~of~~ claim ~~12~~10, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

~~14~~12. The VEGF antagonist for use according to ~~of~~ claim ~~13~~11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

~~15. Use of a VEGF antagonist in the manufacture of a medicament for use in a method of treating an angiogenic eye disorder in a patient, where the treatment 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.~~

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Submission number	3196784
Application number	EP12700590.8
Date of receipt	17 December 2014
Receiving Office	European Patent Office, The Hague
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Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (1 p.) CLMS-1.pdf\N400458EP DXP amended claims - clean - Dec 2014.pdf (2 p.) ep-sfd-request.xml EXRE3-1.pdf\N400458EP DXP response Dec 14.pdf (6 p.) CLMS-HWA-1.pdf\N400458EP DXP amended claims - tracked - Dec 2014.pdf (3 p.)
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Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Anonymous third party observation regarding EP 12700590.8

This is a Third Party Observation pursuant to Article 115 EPC in respect of pending European Patent Application EP12700590.8/2663325 (hereinafter "application") filed on 11 January 2012 in the name of Regeneron Pharmaceuticals, Inc.

The subject matter of the set of claims as filed on 17 December 2014 and currently pending in the application is not patentable under the terms of Articles 52-57 EPC.
Furthermore, the claimed subject matter is not disclosed in the application in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

I. Pertinent Documents

In the following it is referred to document *D13* cited as such in the Examination Procedure, as well as documents *OBS1-OBS8*, which are considered highly relevant with regard to patentability

of the claimed subject matter, all of which represent prior art according to Article 54(2) EPC.

D13: XP002674126

OBS1: Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008

OBS2: Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008

OBS3: Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007

OBS4: WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119

OBS5: Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8

OBS6: Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009

OBS7: Mousa and Mousa, Biodrugs 2010; 24(3); 183-194

OBS8: Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

II. Claims pending in the application

Claim 1 is the sole independent claim currently pending in the application and relates to:

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 **[feature a]**
followed by
- two or more secondary doses of the VEGF antagonist **[feature b]**,
followed by
- one or more tertiary doses of the VEGF antagonist **[feature c]**;
wherein
- each secondary dose is administered 4 weeks after the immediately preceding dose **[feature b1]**;
wherein
- each tertiary dose is administered 8 weeks after the immediately preceding dose **[feature c1]**;
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 **[feature d]**;
and wherein
- the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1 **[feature e]**.

The remaining dependent claims will be referred to in the respective passages below, if applicable.

III. Novelty of the Subject Matter of Claims 1-12

The subject matter of independent claim 1 is not novel over documents *D13*, *OBS1* and *OBS2*.

Independent claim 1 is a second medical use claim, which use is in a treatment of particular angiogenic eye disorders **[feature d]**, characterized by a particular dosage regimen **[features a - c]** of a specific VEGF antagonist **[feature e]**.

The exact same dosage regimen was used in Regeneron's phase 3 trial "VIEW 2" and in this context was available to the public long before the earliest priority date of 13 January 2011.
Evidence for the public availability of the critical details of the VIEW 2 study is provided by prior art documents *D13*, *OBS1* and *OBS2*:

D13, also cited by the Examining Division in the Examination Procedure, describes at page 2 third paragraph, that Regeneron's phase 3 trial aims *inter alia* at "evaluating VEGF TRAP-Eye dosed [...] 2 mg every 8 weeks (following 3 monthly doses)". Such a dosage regimen is covered by claim 1 as it comes down to administering the VEGF antagonist at week 0 **[feature a]**, week 4 and 8 **[feature b1]** and week 16 **[feature c1]**.

Similarly, this dosage regimen was also presented at the 2008 Retina Society Meeting as can be seen from the table at page 29 of *OBS1*, which shows a dosage regimen (row labeled "2.0 mg q8 wks") falling within the definition of that recited in claim 1.

A dosage regimen as claimed is furthermore foreseen in the "Descriptive Information" of this VIEW 2 Clinical Trial, available online in its version of 17 March 2008 (see the third Intervention "Arm 3" at page 2 of *OBS2*).

While in the above cited documents (*D13*, *OBS1*, *OBS2*) the tested compound is denominated "VEGF TRAP-Eye", this designation was known at the priority date of the application for a person skilled in the art as a synonym for "aflibercept" which is encoded by SEQ ID NO:1. Importantly, structural information concerning VEGF TRAP-Eye/aflibercept was at the disposal of the person skilled in the art since 2006, as is apparent from documents *OBS3-OBS8* as follows:

OBS3 is a quality report published on 7 November 2007 by the applicant Regeneron. Such a quality report as required by the US Security and Exchange Commision is immediately available on the internet.

In particular at page 15 and 17 of *OBS3* "VEGF TRAP" is identified as "aflibercept" and at page 19 it is stated that "VEGF TRAP-Eye is a form of the VEGF TRAP [...] suitable for direct injection into the eye". Comparable information is also contained in *OBS8.* From here it is clearly apparent that VEGF TRAP-Eye is aflibercept.
The fact that these two terms are synonym is also acknowledged by the Examining Division (see e.g. item 5 of the Communication dated 21 August 2014).

Knowing that the compound tested in the VIEW 2 trial publicized by *D13* and *OBS1-OBS2* is aflibercept, the person skilled in the art also was in a position to obtain the relevant structural information as such information was available, e.g. from:

OBS4, which is a 2006 report of the WHO that discloses on pages 118 and 119 the chemical structure, i.e. the amino acid sequence of aflibercept, which
- comprises the three elements aa 27-129, aa 130-231 and aa 232-457 of SEQ ID NO:2 of the present application that are characteristic for VEGFR1R2-FcΔC1(a) (as specified in par. [0023] of the specification of the present application), and
- is encoded by SEQ ID NO:1 of the present application **[feature e]**.

Of note, this peptide sequence of aflibercept is identical with the sequence of the particular VEGF antagonist of claim 7 having an amino acid sequence defined by residues 27 to 457 of SEQ ID NO:2 of the application.

Additionally, also documents *OBS5-OBS7* represent the knowledge of a person skilled in the art with respect to the structure of VEGF TRAP-Eye/aflibercept, namely:

OBS5 states at page 3, left column, third paragraph that "VEGF TRAP-Eye and aflibercept" (the oncology product) have the same molecular structure" and this reference also discusses the VIEW 2 study, namely its "bimonthly" **[feature c1]** dosage regimen (see page 4, right column, second paragraph and page 5, right column, first paragraph).

Similarly, *OBS6* states at page 1559, right column, that "aflibercept [is] also known as a VEGF Trap-Eye" and further outlines the structure of this fusion protein. Interestingly, this review focuses on treatment of diabetic retinopathy hence underlining the comparable requirements for the treatment of the different angiogenic diseases **[feature d]** recited in the pending claims.

Finally, *OBS7* repeats the identity of aflibercept and VEGF Trap-Eye and also points to the VIEW 2 study (see page 187).

From the foregoing, it is apparent that there can be no doubt that the person skilled in the art at the earliest priority date was aware that the compound to be tested in the VIEW 2 trial, which trial used the claimed dosage regimen, is aflibercept and its detailed structure being known since 2006.

In light of the above, the subject matter of claims 1 and 7 can by no means be regarded as novel.

As the subject matter of claims 2-6 consists in a mere subdivision of the different diseases listed in claim 1 **[feature d]**, the ascertained lack of novelty likewise applies to the subject matter of these claims.

Claims 8-10 specify administration routes, namely claim 8 pertains to "topical" or "intraocular" administration (the latter being also the subject matter of claim 9), and claim 10 further specifies "intraocular" as being "intravitreal".
While "intraocular" injection of VEGF Trap-Eye is e.g. disclosed at pages 18 and 19 of *OBS3*, the more specific "intravitreal" administration corresponds to the administration route used in the VIEW 2 trial as it is e.g. apparent from the Official title of the study (see *OBS2*): "A Randomized, Double Masked, Active Controlled, Phase 3 study of the Efficacy, Safety and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)" and the Conclusion section on page 28 of *OBS1*.
The features of claims 8-10 are thus not novel as well.

Claim 11 further specifies with respect to claim 1 that "all doses comprise from about 0.5 mg to about 2 mg" of the VEGF antagonist and claim 12 is restricted to the respective end points with claim 12(a) reciting "0.5 mg" and claim 12(b) reciting "2 mg".
These particular doses are anticipated by the VIEW 2 clinical trial (see *D13*; *OBS1* page 29; and *OBS2*) and thus lacks novelty

Claim 12(a) and (b) further specify that "all doses of the VEGF antagonist comprise 0.5 mg/2 mg of the VEGF antagonist", respectively. The use of constant amounts of aflibercept/VEGF Trap-Eye in the VIEW 2 trial is known from page 29 of *OBS1*.
The features of claim 11 and 12 are thus not novel.

The subject matter of claims 1-12 currently pending in the application thus contravenes Article 54 EPC.

IV. Inventive Step and Sufficiency of Disclosure of the Subject Matter of Claims 8-11 and 12

The alternative potential administration route recited in claim 8 that is not known from *OBS*1-3, i.e. "topical administration" which according to paragraph [0028] of the application is an administration "via eye drops or other liquids, gels, ointment or fluid", though certainly desirable as it would overcome the disadvantages associated with intravitreal injections such as being invasive and thus requiring a skilled specialist. However as this administration route is not supported by any data in the application it is hence to be regarded as an obvious alternative to the intraocular administration that is readily available to a person skilled in the art, i.e. lacks an inventive step.
Even more, the absence of experimental evidence gives rise to the conclusion that topical administration does not provide a solution to the technical problem of treating angiogenic eye disorder with a VEGF antagonist.

Similarly, regarding lower doses of 0.5 mg (claim 12(a)) or between 0.5 and 2 mg (claim 11) it has to be noted that these doses do not appear to contribute to an inventive step of the claimed second medical use.
This because, first, the exact value of 0.5 mg corresponds to the amount also used in the "VIEW 2" and previous Regeneron trials in connection with a monthly dosage regimen and further it is the effective concentration at which Ranibizumab is used in these studies for comparison (see *D13*, *OBS1* and *OBS2*). Therefore the choice of this minimal dose seems to be an obvious one for the person skilled in the art.
Second, the application does not even provide any data of the combination of "0.5 mg" and "bimonthly dosing" **[feature c1]**, so that it is questionable whether this dosage regimen solves the technical problem of providing an improved treatment of angiogenic eye disorders with a VEGF antagonist, at all.

The remarks above with regard to the lack of an inventive step for the subject matter of claims 11 and 12(a), namely that there are no supporting data on file demonstrating the effect of these administration regimens also give rise to a lack of sufficiency of disclosure.

The set of claims currently pending in the application thus also contravenes Articles 56 and/or 83 EPC.

In conclusion, the set of claims pending in European Patent Application EP12700590.8/2663325 does not fulfill the requirements of the EPC and should thus not be allowed by the Examining Division.

Encl: *OBS1-OBS8*

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Directorate	:	1466/M12
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OBS6

REVIEW ARTICLE

Advances in the Medical Treatment of Diabetic Retinopathy

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Proliferative diabetic retinopathy (PDR) remains the leading cause of blindness among working-age individuals in developed countries (1). Diabetic macular edema (DME), another important event that occurs in diabetic retinopathy, is more frequent in type 2 than type 1 diabetes (2). Whereas PDR is the most common sight-threatening lesion in type 1 diabetes, DME is the primary cause of poor visual acuity in type 2 diabetes. Because of the high prevalence of type 2 diabetes, DME is the main cause of visual impairment for diabetic patients (2). In addition, DME is almost invariably present when PDR is detected in type 2 diabetes (3). Neovascularization caused by severe hypoxia is the hallmark of PDR, whereas vascular leakage caused by the breakdown of the blood retinal barrier (BRB) is the main event involved in the pathogenesis of DME (4,5).

STANDARD TREATMENT— Although tight control of both blood glucose levels and hypertension is essential to prevent or arrest progression of the disease, the recommended goals are difficult to achieve in many patients and, consequently, diabetic retinopathy develops during the evolution of the disease. When PDR or clinically significant DME do appear, argon-laser photocoagulation is currently indicated, which the efficacy of has been widely demonstrated (6). However, the optimal period for laser treatment has frequently passed; moreover, it is not uniformly successful in halting visual decline. In addition, argon-laser photocoagulation is associated with moderate visual loss, some diminished visual field, reduced color vision, and reduced contrast sensitivity. The presence of these symptoms led to the prevailing thinking that laser treatment prevents vision loss but rarely results in visual improvement.

Intravitreal corticosteroids have been successfully used in the eyes of patients with persistent DME and loss of vision following the failure of conventional treatment (i.e., focal laser treatment and attention to systemic risk factors). However, reinjections are commonly needed, and there are substantial adverse effects such as infection, glaucoma, and cataract formation (6). In addition, recent reports have shown that focal/grid photocoagulation is more effective and has fewer side effects than intravitreal triamcinolone for DME (7,8).

Vitreoretinal surgery is an expensive and complicated treatment that should be carried out only by vitreoretinal specialists experienced in this procedure, and it is normally reserved for the ultimately blinding complications of PDR, such as severe vitreous hemorrhage and secondary retinal detachment. For these reasons, new pharmacological treatments based on the understanding of the pathophysiological mechanisms of diabetic retinopathy are needed.

The paucity of relevant clinical studies addressed to testing new drugs in diabetic retinopathy is due, in part, to the necessity of long-term studies performed in large cohorts of diabetic patients by means of standardized masked grading of retinal photographs. Although there is no fixed rule, the duration of the trial must be consistent with the natural history of diabetic retinopathy and, consequently, at least 5 years seems to be necessary for separating the behavior of retinopathy in the intervention and control groups. In addition, most clinical trials have been aimed at evaluating the progression of diabetic retinopathy, whereas there have been few studies targeting prevention. All these caveats should be kept in mind when analyzing clinical trials on diabetic retinopathy because they can significantly contribute to false-negative results. The presence of diabetic retinopathy in nondiabetic subjects is another challenge. Wong et al. (9), in a study that included more than 11,000 participants from three population cohorts, provide evidence that with the current fasting plasma glucose cutoff of 7.0 mmol/l used to diagnose diabetes, 7.4–13.4% of nondiabetic patients had diabetic retinopathy. This finding, apart from questioning the current diagnostic criteria of diabetes, suggests a potential limit to the risk reduction for diabetic retinopathy that should be taken into consideration when interpreting the results of clinical trials.

Recently, two pivotal studies have been published regarding the beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy (10–12). These studies fulfill all the main requirements for obtaining a valid result: long-term follow-up (~5 years), a large cohort of diabetic patients, retinopathy assessed by standardized methods, and a significant number of patients without diabetic retinopathy at study entry, thus allowing evaluation of the effectiveness of prevention. In advanced stages of diabetic retinopathy, intravitreous anti–vascular endothelial growth factor (VEGF) agents have emerged as new treatments. These drugs are yet to be approved for diabetic retinopathy treatment, but they are currently used by ophthalmologists in selected cases of PDR and DME (13,14). This article discusses the current state of knowledge concerning these novelties in the medical treatment of diabetic retinopathy and highlight areas where further studies and evidence are required.

FENOFIBRATE— Fenofibrate is a peroxisome proliferactor–activated receptor (PPAR)-α agonist indicated for the treatment of hypertriglyceridemia and mixed dislipidemia. Its main action is to lower plasma triglyceride levels, but it also reduces total and LDL cholesterol, raises HDL cholesterol, and decreases

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concentration of small LDL cholesterol particles and apolipoprotein B (15). Recently, Keech et al. (10) have reported results concerning laser treatment for diabetic retinopathy from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. The main aim of this randomized controlled trial was to assess whether long-term lipid-lowering therapy using fenofibrate (a PPAR-α agonist) could reduce the need for laser treatment in a large cohort (n = 9,795) of type 2 diabetic patients. The average follow-up was 5 years, and the end point was the need for laser treatment (a tertiary end point of the main study). In an intention-to-treat analysis, fenofibrate (200 mg once daily) reduced the frequency of laser treatment for macular edema by 31% and for proliferative retinopathy by 30%. In addition, in a substudy performed on patients in whom retinal status was graded by fundus photography, fenofibrate was able to reduce the progression of existing retinopathy. Although this study has some limiting factors (16,17), the substantial benefits obtained from reducing the need for laser treatment argue for consideration of using fenofibrate in the management of diabetic retinopathy. However, our poor knowledge of the mechanisms involved in its beneficial effects in diabetic retinopathy might limit its potential impact on clinical practice. Theoretically, another PPAR-α apart from fenofibrate can also be beneficial for diabetic retinopathy; however, at present this has been only demonstrated with fenofibrate.

The rationale for FIELD was that elevated lipid levels in systemic circulation constitute a risk factor for diabetic retinopathy; therefore, long-term lipid-lowering therapy with fenofibrate could reduce the progression of diabetic retinopathy and the need for laser treatment in patients with type 2 diabetes. However, no relationship between serum lipids and the appearance or progression of diabetic retinopathy was detected. This is in agreement with other prospective studies showing that serum lipids are unrelated to the progression of diabetic retinopathy or the development of PDR (18,19). In addition, the Collaborative Atorvastatin Diabetes Study (CARDS), a randomized controlled trial of 2,830 patients with type 2 diabetes, did not find atorvastatin to be effective in reducing diabetic retinopathy progression (20). However, this study was limited by substantial missing data (only 65% of patients had retinopathy status recorded at baseline) and lack of photographic grading for diabetic retinopathy. Another randomized trial, the ACCORD-EYE study that is now in progress, could shed light on this issue (21). In this study, the effects of lipid control (statin vs. fenofibrate added to a statin) on the progression of diabetic retinopathy will be evaluated. There will be 4,065 participants recruited to the study at baseline for whom fundus photographs will be taken within 4 months of randomization and again 4 years later. Although in the FIELD study there was no relationship between the quantitative levels of serum lipids and diabetic retinopathy, it is unknown whether the effectiveness of fenofibrate in modulating the qualitative properties of lipoproteins (i.e., reducing remnants and small dense LDL particles) can contribute to its beneficial effects. In addition, it should be noted that the mechanisms regulating intraretinal lipid transport rather than serum levels might be more important in the pathogenesis of diabetic retinopathy. In this regard, we have recently shown that apolipoprotein A1 (apo-A1) is overexpressed in the retina of diabetic patients (22). Apo-A1 is a key factor for the intraretinal transport of lipids, thus preventing lipid deposition and lipotoxicity, and it is also a potent scavenger of reactive oxygen species. Therefore, apo-A1 could play an important role in protecting the retina from oxidative stress. These findings have led us to hypothesize that the retinas from diabetic patients have a higher content of apo-A1 as a protective mechanism; consequently, patients with less capacity for apo-A1 production by the retina will be more prone to develop lipid deposition (hard exudates) and retinal damage induced by oxidative stress. Fenofibric acid was shown to enhance transcription of the gene of apo-A1 in the liver (23), macrophages, and fibroblasts (24), but whether this is also true at the retinal level remains to be elucidated.

Other nonlipidic mechanisms by which fenofibrate could be effective in preventing or arresting diabetic retinopathy might be the following:

1) PPAR-α is present in endothelial cells (25), and its activation by means of PPAR-α agonists has recently been shown to inhibit expression of VEGF receptor 2 (VEGFR2) and neovascularization in human umbilical endothelial cells (26). Varet et al. (27) have demonstrated that fenofibrate inhibits angiogenesis in vitro and in vivo as well as basic fibroblast growth factor–induced angiogenesis in vivo. In addition, in cells derived from human ovarian cancer, clofibric acid (a PPAR-α agonist) downregulates VEGF expression (28). Apart from its antiproliferative effects, fenofibrate inhibits the apoptosis induced by high glucose concentrations in human umbilical endothelial cells (29). Moreover, it has been demonstrated that fenofibrate prevents the apoptosis of human retinal endothelial cells induced by serum deprivation through a PPAR-α–independent but AMP-activated protein kinase–dependent pathway (30). This activation of the AMP-activated protein kinase pathway in endothelial cells could lead to an increase in endothelial nitric oxide synthase phosphorylation and nitric oxide production, thus resulting in beneficial effects on endothelial function (31).
2) PPAR-α is associated with anti-inflammatory and antioxidant activity (32). It has been reported that PPAR-α activation induces the expression and activation of antioxidant enzymes, such as superoxide dismutase and glutation peroxidase (33), and that activation of PPAR-α induces apoptosis of human monocyte–derived macrophages (34). In addition, PPAR-α activators inhibit the expression of vascular cell adhesion molecules on the endothelium (35). This effect might be useful in preventing leukostasis (the inappropriate adherence of leukocytes to the endothelium), which is essential in the pathogenesis of PDR.
3) PPAR-α activation also has a neuroprotective effect (33,36). This could be important in preventing neuroretinal degeneration, an early and crucial event that occurs in diabetic retinopathy even before vascular abnormalities can be detected (37).
4) The breakdown of the BRB, caused by the disruption of tight junctions and subsequent leakage, is the main factor accounting for DME (6). Because of the notable effect of fenofibrate in preventing DME progression, it would be worthwhile to explore whether fenofibrate is able to reduce the increased permeability that exists in diabetic retinopathy.

Future research on the potential effects of fenofibrate in all these areas will be essential for understanding its beneficial effects in diabetic retinopathy, and it will also be critical for using this drug as an adjunct in the management of diabetic retinopathy.

BLOCKING THE RENIN-ANGIOTENSIN SYSTEM — Observational and clinical trials have shown that blood pressure is an important modifiable risk factor for diabetic retinopathy and that lowering high blood pressure significantly reduces the development and progression of retinopathy in both type 1 and type 2 diabetic patients (38,39). The blockade of the renin-angiotensin system (RAS) with an ACE inhibitor or by using angiotensin II type 1–receptor (AT1-R) blockers is one of the most used strategies for hypertension treatment in diabetic patients. Apart from the kidney, the RAS system is expressed in the eye (40). In addition, there is growing evidence that RAS activation in the eye plays an important role in the pathogenesis of diabetic retinopathy (40). Therefore, apart from lowering blood pressure, the blockade of the RAS could also be beneficial per se in reducing the development and progression of diabetic retinopathy.

The major components of RAS have been identified in ocular tissues and are overexpressed in the diabetic retina. Angiotensin II (AT) binds and activates two primary receptors, AT1-R and AT2-R. In adult humans, activation of the AT1-R expressed in endothelial cells and pericytes dominates the pathological states (40). AT1-R activation by AT produced by the retina stimulates several pathways involved in the pathogenesis of diabetic retinopathy such as inflammation, oxidative stress, cell proliferation, pericyte migration, remodelling of extracellular matrix by increasing matrix metalloproteinases, angiogenesis, and fibrosis (40). The RAS is upregulated concomitant with hypoxia-induced retinal angiogenesis and is linked to AT-mediated induction of inflammatory mediators and growth factors, including VEGF and platelet-derived growth factor (40,41). In addition, AT1-R activation by AT promotes leukostasis and neurodegeneration (40), two key elements in the pathogenesis of diabetic retinopathy. Most of these pathogenic actions are inhibited or attenuated by pharmacological blockade of the RAS either at levels of ACE or the AT receptors and are accompanied by downregulation of VEGF and VEGFR-2 (40). Recently, Kim et al. (42) have shown that perindopril (an ACE inhibitor) attenuates VEGF-mediated BRB breakdown in rats with streptozotocin-induced diabetes. In addition, it is also worthy of mention that candesartan inhibited retinal accumulation of the advanced glycation end product pentosidine in spontaneously diabetic Torii rats (43). Apart from reducing microvascular disease, there is growing evidence pointing to neuroprotection as a relevant mechanism involved in the beneficial effects of angiotensin receptor blockers in diabetic retinopathy (44–46).

On these experimental bases, it would be reasonable to postulate that RAS blockade can promote higher beneficial effects in diabetic retinopathy than other antihypertensive agents. However, studies in type 2 diabetic patients with hypertension suggest that ACE inhibitors and angiotensin receptor blockers are not superior in preventing or arresting diabetic retinopathy to other drugs equally effective in reducing blood pressure such as the β-blocker atenolol (47) or calcium channel blocker nisoldipine (48). These prospective randomized studies suggest that lowering blood pressure seems to be much more important than the potential effect of RAS blockade in the diabetic eye. However, the question concerning the potential effect of RAS blockers in normotensive diabetic patients remains to be elucidated. In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID), it was reported that in normotensive patients (blood pressure ≤140/90 mmHg), either normoalbuminutic (85% of patients) or microalbuminuric, lisinopril (an ACE inhibitor) had no effect in reducing the incidence of diabetic retinopathy but decreased its progression by two or more grades and decreased the progression to PDR (49). However, these results have been criticized because the placebo group had significantly higher levels of mean A1C than the treatment group. In fact, after adjusting for A1C, the observed differences in progression by two levels and progression to PDR disappear and only the progression by one level remained significant. Other limiting factors of this study were the short period of follow-up (2 years) and the fact that diabetic retinopathy was not the primary end point of the study. Therefore, although the EUCLID study supported the idea of an additional benefit of ACE inhibitors on diabetic retinopathy progression, it was underpowered for the eye-related outcome measures used. Furthermore, in the normotensive type 2 diabetic patients of the Appropriate Blood Pressure Control in Diabetes (ABC) study, Schrier et al. (50) showed that intensive blood pressure control decreased the progression of diabetic retinopathy. However, the results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent. Therefore, the specific antihypertensive agent again appears to be less important than the achievement of the lower blood pressure values.

The Diabetic Retinopathy Candesartan Trials (DIRECT) program was therefore designed to answer the question of whether the blockade of RAS with AT1-R blocker candesartan could prevent the incidence and progression of retinopathy in type 1 and type 2 diabetes independent of lowering blood pressure (11,12). This program consisted of three randomized double-blind placebo-controlled parallel-group studies: *1*) a primary prevention study involving 1,241 type 1 diabetic patients without diabetic retinopathy (DIRECT-Prevent 1), 2) a secondary prevention study involving 1,905 type 1 diabetic patients with diabetic retinopathy (DIRECT-Protect 1), and *3*) a secondary prevention study involving 1,905 type 2 diabetic patients with diabetic retinopathy (DIRECT-Protect 2). In each trial, patients were randomized to receive candesartan (16–32 mg/day) or placebo and the median follow-up was 4.7 years. Patients with type 1 diabetes were eligible for inclusion if they were normoalbuminuric and normotensive (blood pressure ≤130/85 mmHg). For patients with type 2 diabetes, the inclusion criteria were normoalbuminuria and either normal blood pressure without antihypertensive therapy or blood pressure ≤160/90 mmHg during treatment. The primary end point was the incidence of diabetic retinopathy in the primary prevention study and progression of diabetic retinopathy in the secondary prevention studies. In the DIRECT-Prevent 1 study, a nonsignificant reduction (18% relative risk reduction; $P = 0.051$) in the risk of incidence of diabetic retinopathy was observed. However, in a post hoc analysis in which the primary end point was changed from a two-step increase to at least a three-step increase in the ETDRS scale, a significant difference was detected (35% relative risk reduction; $P = 0.003$). This beneficial effect was attenuated but still significant af-

ter the data were adjusted for duration of diabetes, A1C, and systolic blood pressure (26% relative risk reduction; $P = 0.046$) (11). In DIRECT-Protect 1, an identical progression of diabetic retinopathy was found in the placebo and in the candesartan groups, thus suggesting that candesartan is not effective in preventing diabetic retinopathy progression (11). DIRECT-Protect 2 showed a nonsignificant reduction in the progression of diabetic retinopathy (13% relative risk; $P = 0.20$). However, a significant increase in diabetic retinopathy regression was observed (34%, $P = 0.009$), this effect being more evident in patients with mild retinopathy (12). Thus, although the prespecified primary end point was not reached in the DIRECT program, data analysis suggests an overall beneficial effect of candesartan in diabetic retinopathy.

The DIRECT results should be compared with the Action in Diabetes and Vascular Disease (ADVANCE) study, which included 11,140 type 2 diabetic patients (51). In this study, patients randomized to intensive glucose control with glicazide (modified release), as well as other drugs required to achieve A1C ≤6.5% and an ACE inhibitor–diuretic combination (perindopril-indapamide), presented the same 4-year incidence or progression of diabetic retinopathy as the placebo group. These results suggest the possibility that candesartan but not ACE inhibitors might have beneficial effects in diabetic retinopathy. However, it should be noted that unlike DIRECT, ADVANCE did not use standardized retinal photography and there was a lower rate of progression of diabetic retinopathy, thus limiting the power of the study to detect any moderate effects of intervention on microvascular eye disease.

INTRAVITREAL ANTI-VEGF AGENTS— VEGF has been identified as having a major role in the genesis of diabetic retinopathy, with increased levels in animals with experimental diabetes and in the vitreous of patients with diabetic retinopathy. Intravitreal VEGF administration in experimental animals duplicates many features of diabetic retinopathy. Thus, agents that attenuate VEGF action are very attractive because they are able to reduce permeability and neovascularization, the hallmarks of DME and PDR, respectively (4,52).

In general, systemically administered drugs reach the retinochoroidal tissue via blood circulation. However, because the BRB limits the influx of drugs into the retina, large amounts of the drug must be administered to maintain therapeutic concentrations. Regarding anti-VEGF agents, this would lead to systemic inhibition of angiogenesis, which could compromise critical vascular response to ischemic events in diabetic patients with cardiovascular, cerebrovascular, or peripheral vascular disease. Moreover, hypertension and proteinuria (two surrogate markers of systemic VEGF inhibition) as well as the impairment of wound healing are other potential consequences of blocking VEGF and would be particularly worrying to the diabetic population (14). By contrast, the local administration of anti-VEGF agents into the eye by means of intravitreal injections would avoid systemic adverse effects. However, this is invasive and a skilled specialist is required. In addition, in order to maintain effective levels, frequently repeated injections would be necessary, thus increasing local complications such as endophthalmitis, vitreous hemorrhage, retinal detachment, and traumatic cataract. Furthermore, although the eye is thought of as a closed and self-contained system, anti-VEGF drugs injected into the vitreous cavity pass into systemic circulation to varying degrees and could potentially cause the systemic adverse effects mentioned previously (14,52). At present four anti-VEGF agents are available: pegaptamib sodium (macugen; Pfizer), ranibizumab (lucentis; Genentech/Novartis), bevacizumab (avastin; Genentech), and aflibercept (Regeneron Pharmaceuticals/sanofi-aventis).

Pegaptanib is a PEGylated (i.e., conjugated to polyethylene glycol) neutralizing RNA aptamer with an extremely high affinity for isoform 165 of VEGF ($VEGF_{165}$), which is the isoform that participates in pathological but not physiological neovascularization (53). Aptamers are modified nucleotides composed of single-stranded nucleic acids that adopt a specific three-dimensional conformation, allowing them to bind with high specificity and affinity to molecular targets in a manner similar to that of monoclonal antibodies. An important feature of aptamers is that they do not exhibit immunogenicity. Pegaptamib was approved by the U.S. Food and Drug Administration (FDA) for treatment of exudative (wet or neovascular) age-related macular disease (AMD) in December 2004.

Ranibimizumab is a full-length monoclonal antibody directed against VEGF. In contrast to pegaptamib, ranimizumab inhibits the biological activity of all isoforms of human VEGF and could be immunogenic. The FDA approved ranibizumab for wet AMD in June 2006.

Bevacizumab is an anti-VEGF agent similar to ranibizumab and was approved by the FDA in February 2004 for the treatment of disseminated colorectal cancer but not licensed for intraocular use. Nevertheless, intravitreal injection of bevacizumab has become a current off-label treatment by ophthalmologists for neovascular AMD because although it seems to be as effective as pegaptamib or ranimizumab, it is much cheaper.

Aflibercept, also known as a VEGF Trap-Eye because of its ability to block all six VEGF proteins (VEGF-A to VEGF-B as well as placental growth factor), is a fusion protein comprised of segments of the extracellular domains of human VEGF receptors 1 (VEGFR1) and 2 (VEGFR2) fused to the constant region (Fc) of human IgG. Aflibercept is currently being used in clinical trials for both exudative AMD and DME. Aflibercept has a higher binding affinity than other anti-VEGF agents. This higher binding affinity translates into greater activity at lower biological levels and, consequently, a longer duration of action.

The results of prospective clinical trials using pegaptanib and ranibizumab in patients with AMD have been very impressive and have led to the design of specific trials for DME and PDR. At present, only a prospective double-blind multicenter dose-ranging controlled trial has been reported in diabetic patients (54). In this study 172 patients with DME were included, and the patients randomized to receive repeated intravitreal pegaptamib showed better visual outcomes ($P = 0.03$), were more likely to show a reduction in retinal thickness ($P = 0.02$), and needed less additional focal laser ($P = 0.04$) at follow-up (36 weeks) than patients who received intravitreal sham injections. Retrospective data analysis of the eyes of 16 patients with PDR also showed regression of neovascularization (55).

Uncontrolled studies using ranibizumab and bevacizumab have also found a rapid regression of retinal neovascularization, improvement of visual acuity, and decrease of retinal thickness in DME, even in nonresponders to conventional treatment (14,56). However, the response to treatment of DME by VEGF blockade is

not prolonged and is subject to significant variability. This is in distinct contrast to the rapid response of those with both iris and retinal neovascularization in PDR and of those with choroidal neovascularization in wet AMD (57). Interestingly, when the outcomes of intravitreal bevacizumab treatment of DME were compared with those of intravitreal cortisone (triamcinolone acetonide), better outcomes in terms of reduction of foveal thickness and visual results were found with triamcinolone (58). The extent to which VEGF blockade is beneficial for DME is currently being investigated in prospective clinical trials. Apart from their potential as isolated treatments for PDR and DME, intravitreal anti-VEGF agents, in particular bevacizumab, have been shown to be useful in increasing the short-term response to panretinal photocoagulation in high-risk PDR and also seem to be efficacious and safe as an adjuvant treatment to vitrectomy in severe PDR or vitreous hemorrhage (56). This is because intravitreal anti-VEGF agents reduce active neovascularization and vitreous hemorrhage, thus allowing a safe and efficient panretinal photocoagulation or pars plana vitrectomy to be performed while minimizing the risk of complications. Aflibercept has been recently tested in an exploratory study performed in five patients with DME (59). In this study, using a single intravitreal injection, Trap-Eye was well tolerated and preliminary evidence of bioactivity was detected. Taken together, these promising results present a new scenario in the management of diabetic retinopathy. Nevertheless, larger studies investigating not only the effectiveness but also the systemic adverse effects of these agents in the diabetic population are still needed.

It is possible that a drug with more extensive and nonspecific anti-VEGF activity, such as pan-VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept), could be more effective than a drug such as pegaptamib that selectively targets $VEGF_{165}$. In this regard, pegaptamib is substantially less effective than ranibizumab in AMD treatment. By contrast, given that $VEGF_{165}$ plays an essential role in pathological but not physiological neovascularization, pegaptanib could be the best option for avoiding systemic adverse effects in diabetic patients. In addition, long-term intravitreous injections of pan-VEGF inhibitors could lead to retinal neurodegeneration and an increased risk of circulation disturbances in the choriocapillaris (60). However, the theoretical advantage of selective blocking of $VEGF_{165}$ by pegaptamib in terms of both systemic and local side effects remains to be demonstrated in head-to-head clinical trials.

CONCLUDING REMARKS AND FUTURE RESEARCH — Tight control of blood glucose levels and hypertension remains the key element for preventing or arresting diabetic retinopathy. However, two drugs (fenofibrate and candesartan), originally not designed for treatment of diabetic retinopathy, have become new adjuncts in its management. The information drawn from clinical trials indicates that in normotensive diabetic patients, candesartan reduces the incidence of diabetic retinopathy in those with type 1 diabetes and favors diabetic retinopathy regression only in type 2 diabetic patients with mild retinopathy. By contrast, fenofibrate, which has only been tested in type 2 diabetes, has no effect on the incidence of diabetic retinopathy. However, it reduces the progression of existing diabetic retinopathy, thus lessening the need for laser treatment in both DME and PDR, and this beneficial effect is unrelated to changes in serum lipids. Therefore, it would be reasonable to recommend candesartan for type 1 diabetic patients (with or without hypertension) at high risk to develop diabetic retinopathy and for type 2 diabetic patients with mild retinopathy, whereas fenofibrate seems to be a good option for type 2 diabetic patients (with or without dyslipemia) with a wide range of diabetic retinopathy stages (from mild to severe nonproliferative diabetic retinopathy). In addition, the benefit on diabetic retinopathy shown by fenofibrate and candesartan should be considered an extra value when treating dyslipemia and hypertension in diabetic patients. Nevertheless, the mechanisms by which candesartan and, in particular, fenofibrate exert their reported benefits need to be elucidated before these drugs can be launched (alone or in combination) as new tools in the management of diabetic retinopathy. Another question needing specific research is whether such treatments could be administered topically and directly into the eye in order to increase the benefits in diabetic retinopathy.

In advanced stages of diabetic retinopathy, intravitreal delivery of anti-VEGF agents are currently used by many ophthalmologists despite the lack of phase 3 studies supporting their effectiveness and safety. This is due to the successful results obtained in wet AMD and the promising preliminary data in diabetic retinopathy. Intravitreal injection permits antiangiogenic drugs to effectively reach the retina and theoretically overcomes the problem of the systemic blockade of angiogenesis. However, this is an invasive procedure that can have complications such as endophthalmitis and retinal detachment and could even have deleterious effects for the remaining healthy retina. This is especially important in diabetic patients for whom long-term administration is expected. Apart from local side effects, anti-VEGF agents could also produce systemic complications because of their capacity to pass into systemic circulation. The effectiveness and safety of intravitreal anti-VEGF agents are being evaluated in several clinical trials. Meanwhile, in order to minimize systemic adverse effects, it seems reasonable to avoid long-term treatment with anti-VEGF agents for patients with hypertension, proteinuria, renal failure, cardiovascular disease, and foot lesions with wound healing impairment.

A future scenario will involve using a combination of anti-VEGF agents and laser photocoagulation or combining antiangiogenic agents aimed at different steps of angiogenic cascade. This would probably be more successful than single-molecule–specific approaches, would permit a decrease in the frequency of dosing, and would reduce adverse effects. Although it is premature at this stage to advocate such maneuvers, these aspects are certainly worth pursuing in future studies because they may suggest attractive new strategies for improving the treatment of diabetic retinopathy. However, it should be emphasized that, at present, the milestones in diabetic retinopathy treatment are the optimization of blood glucose levels, lowering of blood pressure, and regular fundoscopic screening.

In summary fenofibrate, candesartan, and anti-VEGF agents are now in the armamentarium for diabetic retinopathy treatment. Ophthalmologists and physicians treating diabetic patients should be aware of the potential usefulness of these drugs and work together not only in future research but also in establishing clinical guidelines that will include these newer medical treatments for diabetic retinopathy. Only such coordinated action, as well as competent strategies targeting prevention, will be effective in reducing

the burden and improving the clinical outcome of this devastating complication of diabetes.

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OBS 1

VEGF Trap-Eye in Wet AMD
CLEAR-IT 2: Summary of One-Year Key Results

Presented at 2008 Retina Society Meeting
Scottsdale, Arizona
September 28, 2008

A Phase 2, Randomized, Controlled
Dose- and Interval-Ranging Study
of Intravitreal VEGF Trap-Eye
in Patients With Neovascular,
Age-Related Macular Degeneration

CLEAR-IT 2: Rationale

- Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD
  - Improvement in visual acuity is now an achievable goal of treatment
- A potential limitation of anti-VEGF therapy is the unpredictable durability of vision gain initially achieved with monthly dosing when the treatment interval is prolonged
- VEGF Trap-Eye is a novel anti-VEGF therapy with high binding affinity for VEGF-A and placental growth factor (PlGF)
- CLEAR-IT 2 was designed to assess:
  - Response at 12 weeks to a range of doses administered monthly and quarterly
  - Durability of response with PRN (as-needed) dosing out to 1 year

CLEAR-IT 2: Study Design

Randomized, multicenter, double-masked trial
N=159

0.5 mg q4 wks n=32

2 mg q4 wks n=32

0.5 mg q12 wks n=32

2 mg q12 wks n=32

4 mg q12 wks n=31

Primary endpoint:
Change in Central Retinal Lesion Thickness (CRLT)

Fixed dosing to week 12 (primary endpoint)

Secondary endpoint:
Best-Corrected ETDRS Visual Acuity (BCVA)

PRN dosing to 1 year

Patients were re-dosed at week 12; PRN dosing started at week 16

Study Schedule
(fixed-dosing phase)
Weeks
0
4
8
12
0.5 mg q4 wks
0.5 mg q12 wks
2 mg q4 wks
2 mg q12 wks
4 mg q12 wks
Primary and Secondary
Endpoints
0.5 mg q4 wks VEGF Trap
0.5 mg q12 wks VEGF Trap
2 mg q12 wks VEGF Trap
2 mg q4 wks VEGF Trap
4 mg VEGF Trap

Study Schedule (fixed-dosing phase)

Study Schedule
Weeks
0
4
8
12
16
0.5 mg q4 wks
0.5 mg q12 wks
2 mg q4 wks
2 mg q12 wks
4 mg q12 wks
prn
…1 year
Primary and Secondary Endpoints
0.5 mg q4 wks VEGF Trap
0.5 mg q12 wks VEGF Trap
2 mg q12 wks VEGF Trap
2 mg q4 wks VEGF Trap
4 mg VEGF Trap
6

Baseline Characteristics

(n=157*)	Mean	Range
Age (years)	78.2	53-94
Gender (% M:% F)	38:62	
Disease Duration (months)	3.9	0-67
Lesion Size (mean±SD) in disc areas	3.1±2.12	
Lesion Type: number (%)		
Classic	30 (19.1)	
Predominantly Classic	30 (19.1)	
Minimally Classic	37 (23.6)	
Occult Lesions	60 (38.2)	
Disease Status		
Central Retinal/Lesion Thickness	456 µm	186-1316 µm
Foveal Thickness	327 µm	116-1081 µm
ETDRS BCVA (letters)	56	27-83

*N=159 randomized; n=157 treated

Patient Disposition

No. of Patients	0.5 q4	0.5 q12	2 q4	2 q12	4 q12	All Patients
Screened						301
Randomized	32	32	32	32	31	159
Treated	32	32	31	31	31	157
Completed Wk 52	26	26	29	27	26	134 (84.3%)
Withdrawn by Wk 52	6	6	2	4	5	23 (14.5%)
Reason for Withdrawal						
Non-compliance					1	1 (0.6%)
Subject request	3			2	1	6 (3.8%)
Adverse event				1		1 (0.6%)
Investigator decision	1	1				2 (1.3%)
Sponsor decision	1	1			1	3 (1.9%)
Lost to follow-up		2	1			3 (1.9%)
Death			1		1	2 (1.3%)
Other	1	2		1	1	5 (3.1%) [a]

Primary Endpoint Results: Reported at 2007 Retina Society

At 12 weeks VEGF Trap-Eye:

- Significantly improved mean visual acuity
- Significantly reduced central retinal thickness
- Groups dosed at Baseline and at Week 12 showed improved visual acuity and retinal thickness
  - Effect was not as robust as with monthly dosing
- Maintained effect on visual acuity with a single dose to 8 weeks
- Was generally well tolerated with no drug-related serious adverse events

Number of Doses
Administered
10

Re-dosing Criteria
(starting at week 16)

- Increase in central retinal thickness of ≥100μm as measured by OCT, or;
- A loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or;
- Persistent fluid as indicated by OCT, or;
- New onset classic neovascularization, or;
- New or persistent leak on FA, or;
- New macular hemorrhage

Re-Treatment Outcome

Number of injections over PRN phase*

VEGF Trap-Eye	Mean	Median	Range
0.5 mg q4	2.52	2	0 – 9
2 mg q4	1.55	1	0 – 4
0.5 mg q12	1.84	2	0 – 4
2 mg q12	2.48	3	0 – 5
4 mg q12	1.7	1	0 – 7
All	**2.01**	2	0 – 9

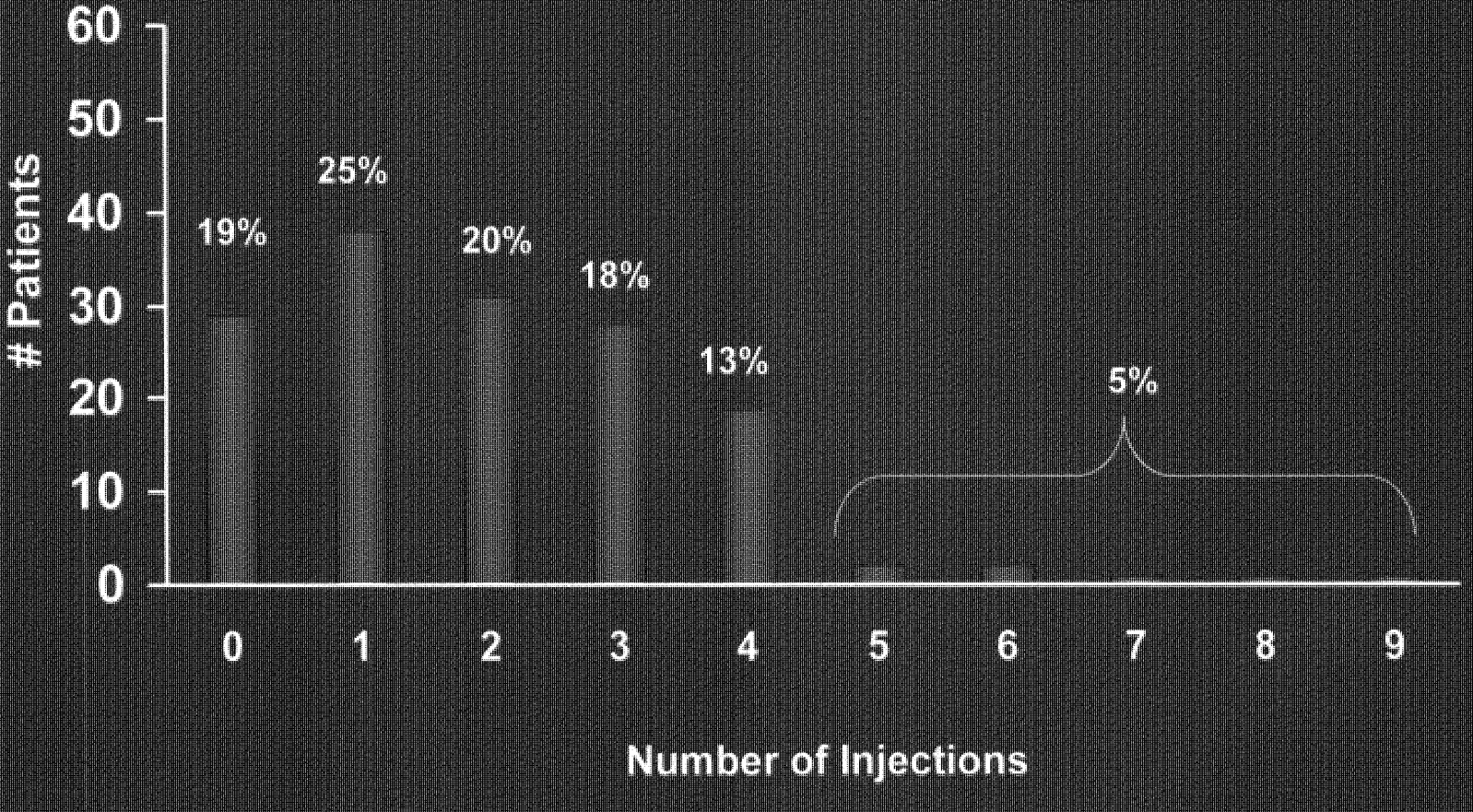
All patients, n=152

* After the week 12 injection through week 52

Re-Treatment Outcome

VEGF Trap-Eye	Mean number of injections over PRN phase (week 12 – 52)	Mean number of days to first injection over PRN phase (week 12 – 52)	Median number of days to first injection over PRN phase (week 12 – 52)
0.5 mg q4			85
2 mg q4			150
0.5 mg q12			86
2 mg q12			86
4 mg q12			111
All			110

Distribution of Injections over PRN Phase
(All groups combined)

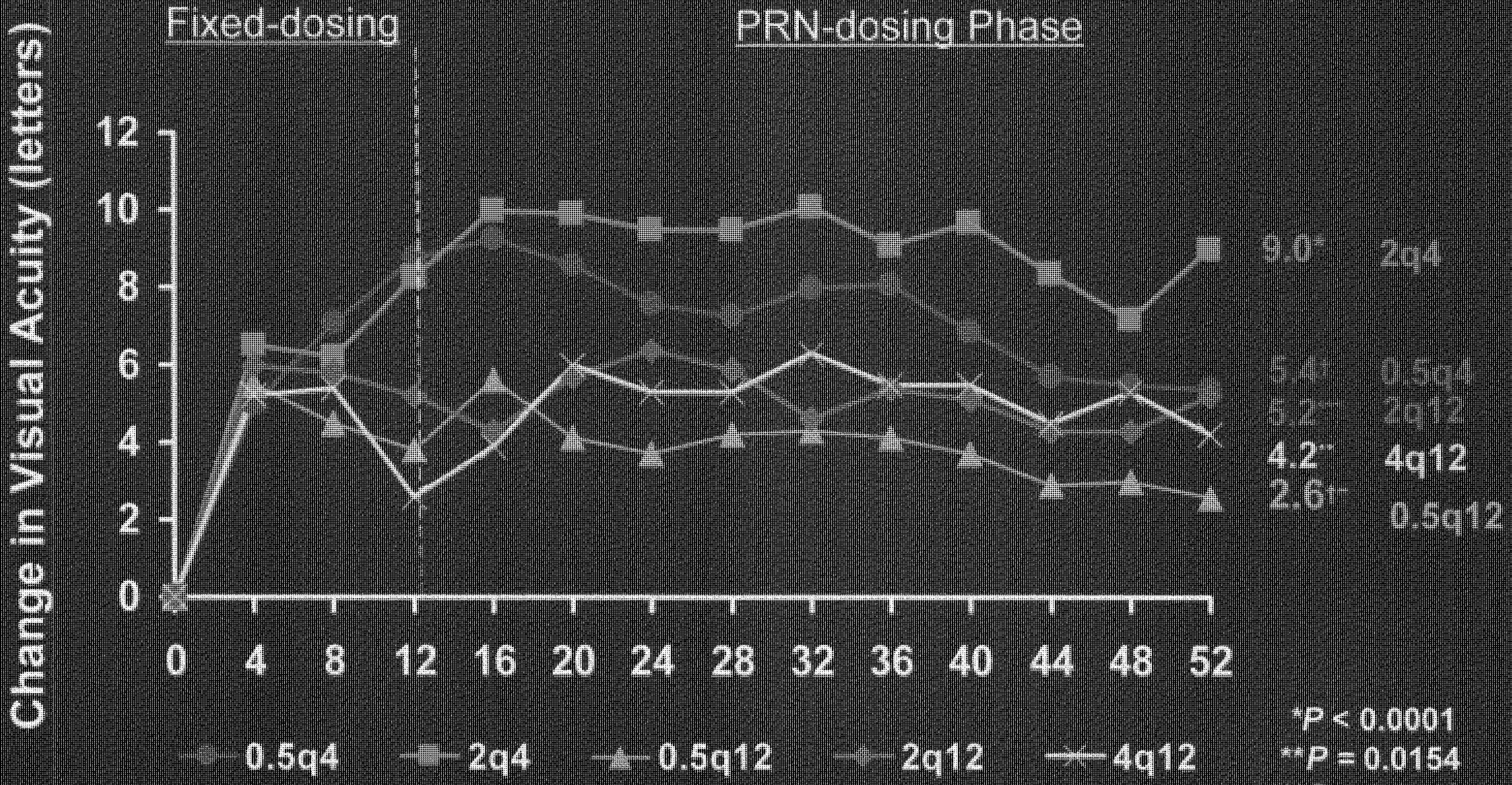


Percent of patients receiving an injection analyzed by number of injections, n=152

Kaplan-Meier Curve
Time to Re-injection (by treatment group)
Time to 1st re-injection
0.5q12
0.5q4
2.0q12
2.0q4
4.0q12
Censored
Median # of days to 1st re-injection in 2.0q4 group = 150
Percent Patients
100
80
60
40
20
0
0
100
200
300
400
Days
15

Mean Change in Visual Acuity
Change in Visual Acuity (letters)
12
10
8
6
4
2
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Fixed-dosing
PRN-dosing Phase
9.0
2q4
5.4
0.5q4
*P < 0.0001
†P = 0.085
0.5 mg q4
2 mg q4
Last Observation Carried Forward (LOCF) analysis; paired t-test: 0.5q4: n=32; 2q4: n=31
16

Mean Change in Visual Acuity



*$P < 0.0001$
**$P = 0.0154$
***$P = 0.0412$
†$P = 0.085$
††$P = 0.344$

LOCF analysis; paired t-test; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

Mean Change in Central Retinal/Lesion Thickness
Fixed-dosing
PRN-dosing Phase
Week
0 4 8 12 16 20 24 28 32 36 40 44 48 52
0 -50 -100 -150 -200 -250
Change in CR/LT (microns)
-109* 0.5q12
-161† 4q12
*P < 0.0001
†P = 0.0002
0.5q4
2q4
0.5q12
2q12
4q12
Posterior Pole Scans; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31
18

Visual Acuity at Week 52
Patients (%)
100%
80%
60%
40%
20%
0%
88%
100%
88%
90%
97%
78%
81%
74%
71%
58%
29%
19%
29%
22%
10%
<15 letters lost
≥ 0 letter gain
≥ 15 letter gain
0.5q4
2q4
0.5q12
2q12
4q12
LOCF analysis; 0.5q4 and 0.5q12 n=32; 2q4, 2q12, and 4q12; n=31
19

Proportion of Patients
With ≥ 20/40 Vision
Patients (%) With
≥20/40 Vision
50%
40%
30%
20%
10%
0%
47%
16%
45%
23%
45%
22%
34%
10%
36%
16%
BL Wk52
BL Wk52
BL Wk52
BL Wk52
0.5q4
2q4
0.5q12
2q12
2q12
4q12
Dose Groups
LOCF analysis: 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31 BL=baseline
20

Fluorescein Angiography 1-Year Outcomes

DARC Reading Center: Definitions

- Total Lesion Size
  - Measurement of entire lesion including the classic and occult neo-vascular component as well as contiguous areas of blood and/or blocked fluorescence and/or serous pigment epithelial detachment (PED)
- Total Active CNV Size
  - Area of visible CNV (classic and/or occult) which demonstrates angiographic evidence of late leakage or pooling of dye
- Classic CNV
  - Area of bright, well-demarcated hyper-fluorescence in early phase, with progressive dye leakage into overlying sub-sensory retinal space in late phase of angiogram (not a measurement of area of leakage, but rather extent of the classic neo-vascular complex)
- Occult CNV
  - Angiogram shows staining or leakage from fibro-vascular PED or hyper-fluorescent leakage at level of RPE that represents late leakage of undetermined source (leakage in late phase without classic CNV or fibro-vascular PED to account for leakage)

Mean Change in Total Lesion Size by Fluorescein Angiography
Change From Baseline (mm²)
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
Fixed-dosing
PRN-dosing Phase
-0.85‡
-0.01†
-0.04‡
-1.00‡
-1.75‡
0.5q12
0.5q4
2q12
4q12
2q4
0
4
12
24
36
48
Week
0.5q4
2q4
0.5q12
2q12
4q12
Lesion Size at Baseline (mm²)
4.9
7.4
5.5
7.6
6.5
*P = 0.04
†P = NS
Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31
23

Mean Change in Total Active CNV Size
by Fluorescein Angiography
Fixed-dosing
PRN-dosing Phase
Week
0
4
12
24
36
48
Change From Baseline (mm²)
2.0
1.0
0
-1.0
-2.0
-3.0
-4.0
-1.35† 0.5q12
-2.59** 4q12
-3.41† 2q4
0.5q4
2q4
0.5q12
2q12
4q12
*P < 0.001
**P < 0.05
†P = ns
CNV Size at baseline (mm²) 4.6 6.9 4.8 6.8 5.6
Mandatory FA only. LOCF analysis. 0.5q4 and 0.5q12: n=32. 2q4, 2q12, and 4q12: n=31
24

Mean Change in Classic CNV Size by Fluorescein Angiography
Fixed-dosing
PRN-dosing Phase
Week
0
4
12
24
36
48
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
Change From Baseline (mm²)
All P values ≤ 0.013
0.5q4
2q4
0.5q12
2q12
4q12
Classic CNV Size at Baseline (mm²)
1.2
1.2
1.8
1.8
1.3
Mandatory FA only; LOCF analysis: 0.5q4 and 0.5q12: n=32; 2q4, 2q12 and 4q12: n=31
25

Safety: Serious Adverse Events

Ocular Serious Adverse Events in the study eye:

- 1 case of culture-negative endophthalmitis / uveitis
  - (deemed not related to study drug)

Systemic Serious Adverse Events:

- None deemed to be drug-related
- 2 deaths
  - Pulmonary hypertension (pre-existing condition)
  - Pancreatic carcinoma
- Arterial Thromboembolic Events (ATE's): 1 case of hemorrhagic stroke
  - Subject had a history of prior stroke

Adverse Events
(Study eye, all groups combined ≥ 5%)

Adverse Event	Number (N=157)	Percent (%)
Conjunctival Hemorrhage	60	38.2
Increased IOP (transient post-injection)	29	18.5
Refraction Disorder	25	15.9
Retinal Hemorrhage	23	14.6
Visual Acuity Reduced (patient reported)	21	13.4
Vitreous Detachment	18	11.5
Eye Pain	15	9.6
Vitreous Floaters	14	8.9
Detachment of Retinal Pigment Epithelium	12	7.6
Retinal Edema	10	6.4
Visual Disturbance	9	5.7
Blepharitis	8	5.1
Cataract nuclear	8	5.1
Subretinal Fibrosis	8	5.1

IOP=intraocular pressure

Conclusions

- Patients received, on average, only two additional injections over 40-week PRN-dosing phase (after a 12-week fixed dosing period)
  - 19% received no additional injections after Week 12
  - 110 days median time to first re-injection
- VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over 1 year
  - Up to +9.0 mean letters gained at week 52
  - Up to -161 microns reduction in central retinal lesion thickness at week 52 as measured by OCT
- Generally well tolerated with no drug-related serious adverse events
  - Most common AE's typical of intravitreal injection

VIEW 1 & VIEW 2 Phase 3 Studies
(Dosing Schedule-Years 1 and 2)

Week 0 4 8 12 16 20 24 28 32 36-51* 52 52 – 96
Capped PRN †

0.5 mg q4 wks
2.0 mg q4 wks
2.0 mg q8 wks‡
Ranibizumab 0.5 mg q4 wks

Primary and Secondary Endpoints Measured

*Continued dosing at their respective intervals
‡After a loading dose period of 3-months
† Capped PRN: minimum injection frequency is q12 weeks

0.5 mg VEGF Trap | 2 mg q4 wks VEGF Trap | 2 mg q8 wks VEGF Trap | 0.5 mg Ranibizumab

OBS 2

View of NCT00637377 on 2008_03_17

ClinicalTrials Identifier: NCT00637377
Updated: 2008_03_17

Descriptive Information

Brief title VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2).

Official title A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD).

Brief summary

This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Active Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (ie, prevention of moderate vision loss) Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52 Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: The proportion of subjects who gain at least 15 letters of vision at Week 52 Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in total NEI VFQ-25 score at Week 52

	Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in CNV area at Week 52 Time Frame: week 52 Safety Issue? Yes
Enrollment	1200 (Anticipated)
Condition	Macular Degeneration
Arm/Group	Arm Label: Arm 3 Experimental n/a
Arm/Group	Arm Label: Arm 1 Experimental n/a
Arm/Group	Arm Label: Arm 2 Experimental n/a
Arm/Group	Arm Label: Arm 4 Active Comparator n/a
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 1 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 2 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 3 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: Ranibizumab Arm Label: Arm 4 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
URL	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
URL	http://www.fda.gov/medwatch/safety.htm
URL	http://www.clinicalstudyresults.org
See also	Click here and search for drug information provided by the FDA
See also	Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product
See also	

Click here to find results for studies related to marketed products

Recruitment Information

Status Not yet recruiting
Start date 2008-03
Last follow-up date 2011-09 (Anticipated)
Criteria

Inclusion Criteria:
1. Signed informed consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye at 4 meters.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria:
1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size >12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
6. Scar or fibrosis making up >50% of the total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. Prior vitrectomy in the study eye.
12. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
13. Any history of macular hole of stage 2 and above in the study eye.
14. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
15. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Gender Both
Minimum age 50 Years
Healthy volunteers No

Administrative Data

Organization name	Bayer
Organization study ID	91689
Secondary ID	EurdaCT No.: 2007-000583-25
Secondary ID	311523
Secondary ID	VIEW 2
Sponsor	Bayer
Collaborator	Regeneron Pharmaceuticals
Health Authority	Switzerland: Ethikkommision

Future Impact of Recently Issued Accounting Standards

In February 2007, the Financial Accounting Standards Board (FASB) issued Statement of Financial Accounting Standards No. (SFAS) 159, *The Fair Value Option for Financial Assets and Financial Liabilities* . SFAS 159 permits entities to choose to measure many financial instruments and certain other items at fair value. The objective is to improve financial reporting by providing entities with the opportunity to mitigate volatility in reported earnings caused by measuring related assets and liabilities differently without having to apply complex hedge accounting provisions. SFAS 159 is effective for financial statements issued for fiscal years beginning after November 15, 2007. We will be required to adopt SFAS 159 effective for the fiscal year beginning January 1, 2008. Our management is currently evaluating the potential impact of adopting SFAS 159 on our financial statements.

In June 2007, the Emerging Issues Task Force issued Statement No. 07-3, *Accounting for Non-refundable Advance Payments for Goods or Services to Be Used in Future Research and Development Activities* (EITF 07-3). EITF 07-3 addresses how entities involved in research and development activities should account for the non-refundable portion of an advance payment made for future research and development activities and requires that such payments be deferred and capitalized, and recognized as an expense when the goods are delivered or the related services are performed. EITF 07-3 is effective for fiscal years beginning after December 15, 2007, including interim periods within those fiscal years. We will be required to adopt EITF 07-3 effective for the fiscal year beginning January 1, 2008. Our management believes that the future adoption of EITF 07-3 will not have a material impact on our financial statements.

Item 3. Quantitative and Qualitative Disclosure About Market Risk

Interest Rate Risk:

Our earnings and cash flows are subject to fluctuations due to changes in interest rates primarily from our investment of available cash balances in investment grade corporate, asset-backed, and U.S. government securities. We do not believe we are materially exposed to changes in interest rates. Under our current policies we do not use interest rate derivative instruments to manage exposure to interest rate changes. We estimate that a one percent unfavorable change in interest rates would result in approximately a $2.2 million and $0.5 million decrease in the fair market value of our investment portfolio at September 30, 2007 and 2006, respectively. The increase in the potential impact of an interest rate change at September 30, 2007, compared to September 30, 2006, is due primarily to increases in our investment portfolio's balance and duration at the end of September 2007 versus September 2006.

Credit Quality Risk:

We have an investment policy that includes guidelines on acceptable investment securities, minimum credit quality, maturity parameters, and concentration and diversification. Nonetheless, deterioration of the credit quality of an investment security subsequent to purchase may subject us to the risk of not being able to recover the full principal value of the security. In the third quarter of 2007, we recognized a $0.8 million charge related to securities that we considered to be other than temporarily impaired.

Item 4. Controls and Procedures

Our management, with the participation of our chief executive officer and chief financial officer, conducted an evaluation of the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 (the "Exchange Act")), as of the end of the period covered by this report. Based on this evaluation, our chief executive officer and chief financial officer each concluded that, as of the end of such period, our disclosure controls and procedures were effective in ensuring that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in applicable rules and forms of the Securities and Exchange Commission, and is accumulated and communicated to our management, including our chief executive officer and chief financial officer, as appropriate to allow timely decisions regarding required disclosure.

There has been no change in our internal control over financial reporting (as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended September 30, 2007 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. Legal Proceedings

From time to time, we are a party to legal proceedings in the course of our business. We do not expect any such current legal proceedings to have a material adverse effect on our business or financial condition.

Item 1A. Risk Factors

We operate in an environment that involves a number of significant risks and uncertainties. We caution you to read the following risk factors, which have affected, and/or in the future could affect, our business, operating results, financial condition, and cash flows. The risks described below include forward-looking statements, and actual events and our actual results may differ substantially from those discussed in these forward-looking statements. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also impair our business operations. Furthermore, additional risks and uncertainties are described under other captions in this report and in our Annual Report on Form 10-K for the year ended December 31, 2006 and should be considered by our investors.

Risks Related to Our Financial Results and Need for Additional Financing

We have had a history of operating losses and we may never achieve profitability. If we continue to incur operating losses, we may be unable to continue our operations.

From inception on January 8, 1988 through September 30, 2007, we had a cumulative loss of $780.1 million. If we continue to incur operating losses and fail to become a profitable company, we may be unable to continue our operations. We have no products that are available for sale and

do not know when we will have products available for sale, if ever. In the absence of revenue from the sale of products or other sources, the amount, timing, nature or source of which cannot be predicted, our losses will continue as we conduct our research and development activities.

We will need additional funding in the future, which may not be available to us, and which may force us to delay, reduce or eliminate our product development programs or commercialization efforts.

We will need to expend substantial resources for research and development, including costs associated with clinical testing of our product candidates. We believe our existing capital resources will enable us to meet operating needs through at least early 2010, without taking into consideration the $200.0 million aggregate principal amount of convertible senior subordinated notes, which mature in October 2008; however, our projected revenue may decrease or our expenses may increase and that would lead to our capital being consumed significantly before such time. We will likely require additional financing in the future and we may not be able to raise such additional funds. If we are able to obtain additional financing through the sale of equity or convertible debt securities, such sales may be dilutive to our shareholders. Debt financing arrangements may require us to pledge certain assets or enter into covenants that would restrict our business activities or our ability to incur further indebtedness and may contain other terms that are not favorable to our shareholders. If we are unable to raise sufficient funds to complete the development of our product candidates, we may face delay, reduction or elimination of our research and development programs or preclinical or clinical trials, in which case our business, financial condition or results of operations may be materially harmed.

We have a significant amount of debt and may have insufficient cash to satisfy our debt service and repayment obligations. In addition, the amount of our debt could impede our operations and flexibility.

We have a significant amount of convertible debt and semi-annual interest payment obligations. This debt, unless converted to shares of our common stock, will mature in October 2008. We may be unable to generate sufficient cash flow or otherwise obtain funds necessary to make required payments on our debt. Even if we are able to meet our debt service obligations, the amount of debt we already have could hurt our ability to obtain any necessary financing in the future for working capital, capital expenditures, debt service requirements, or other purposes. In addition, our debt obligations could require us to use a substantial portion of cash to pay principal and interest on our debt, instead of applying those funds to other purposes, such as research and development, working capital, and capital expenditures.

Risks Related to Development of Our Product Candidates

Successful development of any of our product candidates is highly uncertain.

Only a small minority of all research and development programs ultimately result in commercially successful drugs. We have never developed a drug that has been approved for marketing and sale, and we may never succeed in developing an approved drug. Even if clinical trials demonstrate safety and effectiveness of any of our product candidates for a specific disease and the necessary regulatory approvals are obtained, the commercial success of any of our product candidates will depend upon their acceptance by patients, the medical community, and

third-party payers and on our partners' ability to successfully manufacture and commercialize our product candidates. Our product candidates are delivered either by intravenous infusion or by intravitreal or subcutaneous injections, which are generally less well received by patients than tablet or capsule delivery. If our products are not successfully commercialized, we will not be able to recover the significant investment we have made in developing such products and our business would be severely harmed.

We are studying our lead product candidates, aflibercept, VEGF Trap-Eye, and rilonacept, in a wide variety of indications. We are studying aflibercept in a variety of cancer settings, the VEGF Trap-Eye in different eye diseases and ophthalmologic indications, and rilonacept in a variety of systemic inflammatory disorders. Many of these current trials are exploratory studies designed to identify what diseases and uses, if any, are best suited for our product candidates. It is likely that our product candidates will not demonstrate the requisite efficacy and/or safety profile to support continued development for most of the indications that are to be studied. In fact, our product candidates may not demonstrate the requisite efficacy and safety profile to support the continued development for any of the indications or uses.

Clinical trials required for our product candidates are expensive and time-consuming, and their outcome is highly uncertain. If any of our drug trials are delayed or achieve unfavorable results, we will have to delay or may be unable to obtain regulatory approval for our product candidates.

We must conduct extensive testing of our product candidates before we can obtain regulatory approval to market and sell them. We need to conduct both preclinical animal testing and human clinical trials. Conducting these trials is a lengthy, time-consuming, and expensive process. These tests and trials may not achieve favorable results for many reasons, including, among others, failure of the product candidate to demonstrate safety or efficacy, the development of serious or life-threatening adverse events (or side effects) caused by or connected with exposure to the product candidate, difficulty in enrolling and maintaining subjects in the clinical trial, lack of sufficient supplies of the product candidate or comparator drug, and the failure of clinical investigators, trial monitors and other consultants, or trial subjects to comply with the trial plan or protocol. A clinical trial may fail because it did not include a sufficient number of patients to detect the endpoint being measured or reach statistical significance. A clinical trial may also fail because the dose(s) of the investigational drug included in the trial were either too low or too high to determine the optimal effect of the investigational drug in the disease setting. For example, we are studying higher doses of rilonacept in different diseases after a Phase 2 trial using lower doses of rilonacept in subjects with rheumatoid arthritis failed to achieve its primary endpoint.

We will need to reevaluate any drug candidate that does not test favorably and either conduct new trials, which are expensive and time consuming, or abandon the drug development program. Even if we obtain positive results from preclinical or clinical trials, we may not achieve the same success in future trials. Many companies in the biopharmaceutical industry, including us, have suffered significant setbacks in clinical trials, even after promising results have been obtained in earlier trials. The failure of clinical trials to demonstrate safety and effectiveness for the desired indication(s) could harm the development of the product candidate(s), and our business, financial condition, and results of operations may be materially harmed.

The data from the Phase 3 clinical program for rilonacept in CAPS (Cryopyrin-Associated Periodic Syndromes) may be inadequate to support regulatory approval for commercialization of rilonacept.

We recently submitted a BLA to the FDA for rilonacept in CAPS. However, the efficacy and safety data from the Phase 3 clinical program included in the BLA may be inadequate to support approval for commercialization of rilonacept. The FDA and other regulatory agencies may have varying interpretations of our clinical trial data, which could delay, limit, or prevent regulatory approval or clearance.

Further, before a product candidate is approved for marketing, our manufacturing facilities must be inspected by the FDA and the FDA will not approve the product for marketing if we or our third party manufacturers are not in compliance with current good manufacturing practices. Even if the FDA and similar foreign regulatory authorities do grant marketing approval for rilonacept, they may pose restrictions on the use or marketing of the product, or may require us to conduct additional post-marketing trials. These restrictions and requirements would likely result in increased expenditures and lower revenues and may restrict our ability to commercialize rilonacept profitably.

In addition to the FDA and other regulatory agency regulations in the United States, we are subject to a variety of foreign regulatory requirements governing human clinical trials, marketing and approval for drugs, and commercial sales and distribution of drugs in foreign countries. The foreign regulatory approval process includes all of the risks associated with FDA approval as well as country-specific regulations. Whether or not we obtain FDA approval for a product in the United States, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of rilonacept in those countries.

The development of serious or life-threatening side effects with any of our product candidates would lead to delay or discontinuation of development, which could severely harm our business.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries, and discomforts, to their study doctor. Often, it is not possible to determine whether or not the drug candidate being studied caused these conditions. Various illnesses, injuries, and discomforts have been reported from time-to-time during clinical trials of our product candidates. Although our current drug candidates appeared to be generally well tolerated in clinical trials conducted to date, it is possible as we test any of them in larger, longer, and more extensive clinical programs, illnesses, injuries, and discomforts that were observed in earlier trials, as well as conditions that did not occur or went undetected in smaller previous trials, will be reported by patients. Many times, side effects are only detectable after investigational drugs are tested in large scale, Phase 3 clinical trials or, in some cases, after they are made available to patients after approval. If additional clinical experience indicates that any of our product candidates has many side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, which would severely harm our business.

Our aflibercept (VEGF Trap) is being studied for the potential treatment of certain types of cancer and our VEGF Trap-Eye candidate is being studied in diseases of the eye. There are many

potential safety concerns associated with significant blockade of vascular endothelial growth factor, or VEGF. These serious and potentially life-threatening risks, based on the clinical and preclinical experience of systemically delivered VEGF inhibitors, including the systemic delivery of the VEGF Trap, include bleeding, hypertension, and proteinuria. These serious side effects and other serious side effects have been reported in our systemic VEGF Trap studies in cancer and diseases of the eye. In addition, patients given infusions of any protein, including the VEGF Trap delivered through intravenous administration, may develop severe hypersensitivity reactions or infusion reactions. Other VEGF blockers have reported side effects that became evident only after large scale trials or after marketing approval and large number of patients were treated. These include side effects that we have not yet seen in our trials such as heart attack and stroke. These and other complications or side effects could harm the development of aflibercept for the treatment of cancer or the VEGF Trap-Eye for the treatment of diseases of the eye.

It is possible that safety or tolerability concerns may arise as we continue to test rilonacept in patients with inflammatory diseases and disorders. Like cytokine antagonists such as Kineret ® (Amgen Inc.), Enbrel ® (Immunex Corporation), and Remicade ® (Centocor, Inc.), rilonacept affects the immune defense system of the body by blocking some of its functions. Therefore, rilonacept may interfere with the body's ability to fight infections. Treatment with Kineret ® (Amgen), a medication that works through the inhibition of IL-1, has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking rilonacept. One subject with adult Still's diseases in a study of rilonacept developed an infection in his elbow with mycobacterium intracellulare. The patient was on chronic glucocorticoid treatment for Still's disease. The infection occurred after an intraarticular glucocorticoid injection into the elbow and subsequent local exposure to a suspected source of mycobacteria. One patient with polymayalgia rheumatica in another study developed bronchitis/sinusitis, which resulted in hospitalization. One patient in an open-label study of rilonacept in CAPS developed sinusitis and streptococcus pneumoniae meningitis and subsequently died. In addition, patients given infusions of rilonacept have developed hypersensitivity reactions or infusion reactions. These or other complications or side effects could impede or result in us abandoning the development of rilonacept.

Our product candidates in development are recombinant proteins that could cause an immune response, resulting in the creation of harmful or neutralizing antibodies against the therapeutic protein.

In addition to the safety, efficacy, manufacturing, and regulatory hurdles faced by our product candidates, the administration of recombinant proteins frequently causes an immune response, resulting in the creation of antibodies against the therapeutic protein. The antibodies can have no effect or can totally neutralize the effectiveness of the protein, or require that higher doses be used to obtain a therapeutic effect. In some cases, the antibody can cross react with the patient's own proteins, resulting in an "auto-immune" type disease. Whether antibodies will be created can often not be predicted from preclinical or clinical experiments, and their detection or appearance is often delayed, so that there can be no assurance that neutralizing antibodies will not be detected at a later date — in some cases even after pivotal clinical trials have been completed. Of the clinical study subjects who received rilonacept for rheumatoid arthritis and other indications, fewer than 5% of patients developed antibodies and no side effects related to antibodies were observed. Using a very sensitive test, approximately 40% of the patients in the CAPS pivotal study tested positive at least once for low levels of antibodies to rilonacept.

Again, no side effects related to antibodies were observed and there were no observed effects on drug efficacy or drug levels. However, it is possible that as we continue to test aflibercept and VEGF Trap-Eye with more sensitive assays in different patient populations and larger clinical trials, we will find that subjects given aflibercept and VEGF Trap-Eye develop antibodies to these product candidates, and may also experience side effects related to the antibodies, which could adversely impact the development of such candidates.

We may be unable to formulate or manufacture our product candidates in a way that is suitable for clinical or commercial use.

Changes in product formulations and manufacturing processes may be required as product candidates progress in clinical development and are ultimately commercialized. For example, we are currently testing a new formulation of the VEGF Trap-Eye. If we are unable to develop suitable product formulations or manufacturing processes to support large scale clinical testing of our product candidates, including aflibercept, VEGF Trap-Eye, and rilonacept, we may be unable to supply necessary materials for our clinical trials, which would delay the development of our product candidates. Similarly, if we are unable to supply sufficient quantities of our product or develop product formulations suitable for commercial use, we will not be able to successfully commercialize our product candidates.

Risks Related to Intellectual Property

If we cannot protect the confidentiality of our trade secrets or our patents are insufficient to protect our proprietary rights, our business and competitive position will be harmed.

Our business requires using sensitive and proprietary technology and other information that we protect as trade secrets. We seek to prevent improper disclosure of these trade secrets through confidentiality agreements. If our trade secrets are improperly exposed, either by our own employees or our collaborators, it would help our competitors and adversely affect our business. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our rights are covered by valid and enforceable patents or are effectively maintained as trade secrets. The patent position of biotechnology companies involves complex legal and factual questions and, therefore, enforceability cannot be predicted with certainty. Our patents may be challenged, invalidated, or circumvented. Patent applications filed outside the United States may be challenged by third parties who file an opposition. Such opposition proceedings are increasingly common in the European Union and are costly to defend. We have patent applications that are being opposed and it is likely that we will need to defend additional patent applications in the future. Our patent rights may not provide us with a proprietary position or competitive advantages against competitors. Furthermore, even if the outcome is favorable to us, the enforcement of our intellectual property rights can be extremely expensive and time consuming.

We may be restricted in our development and/or commercialization activities by, and could be subject to damage awards if we are found to have infringed, third party patents or other proprietary rights.

Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties. Other parties may allege that they have

blocking patents to our products in clinical development, either because they claim to hold proprietary rights to the composition of a product or the way it is manufactured or used. Moreover, other parties may allege that they have blocking patents to antibody products made using our *VelocImmune* technology, either because of the way the antibodies are discovered or produced or because of a proprietary position covering an antibody or the antibody's target.

We are aware of patents and pending applications owned by Genentech that claim certain chimeric VEGF receptor compositions. Although we do not believe that aflibercept or the VEGF Trap-Eye infringes any valid claim in these patents or patent applications, Genentech could initiate a lawsuit for patent infringement and assert its patents are valid and cover aflibercept or the VEGF Trap-Eye. Genentech may be motivated to initiate such a lawsuit at some point in an effort to impair our ability to develop and sell aflibercept or the VEGF Trap-Eye, which represents a potential competitive threat to Genentech's VEGF-binding products and product candidates. An adverse determination by a court in any such potential patent litigation would likely materially harm our business by requiring us to seek a license, which may not be available, or resulting in our inability to manufacture, develop and sell aflibercept or the VEGF Trap-Eye or in a damage award.

Any patent holders could sue us for damages and seek to prevent us from manufacturing, selling, or developing our drug candidates, and a court may find that we are infringing validly issued patents of third parties. In the event that the manufacture, use, or sale of any of our clinical candidates infringes on the patents or violates other proprietary rights of third parties, we may be prevented from pursuing product development, manufacturing, and commercialization of our drugs and may be required to pay costly damages. Such a result may materially harm our business, financial condition, and results of operations. Legal disputes are likely to be costly and time consuming to defend.

We seek to obtain licenses to patents when, in our judgment, such licenses are needed. If any licenses are required, we may not be able to obtain such licenses on commercially reasonable terms, if at all. The failure to obtain any such license could prevent us from developing or commercializing any one or more of our product candidates, which could severely harm our business.

Regulatory and Litigation Risks

If we do not obtain regulatory approval for our product candidates, we will not be able to market or sell them.

We cannot sell or market products without regulatory approval. If we do not obtain and maintain regulatory approval for our product candidates, the value of our company and our results of operations will be harmed. In the United States, we must obtain and maintain approval from the United States Food and Drug Administration (FDA) for each drug we intend to sell. Obtaining FDA approval is typically a lengthy and expensive process, and approval is highly uncertain. Foreign governments also regulate drugs distributed in their country and approval in any country is likely to be a lengthy and expensive process, and approval is highly uncertain. None of our product candidates has ever received regulatory approval to be marketed and sold in the United States or any other country. We may never receive regulatory approval for any of our product candidates.

Before approving a new drug or biologic product, the FDA requires that the facilities at which the product will be manufactured be in compliance with current good manufacturing practices, or cGMP requirements. Manufacturing product candidates in compliance with these regulatory requirements is complex, time-consuming, and expensive. To be successful, our products must be manufactured for development, following approval, in commercial quantities, in compliance with regulatory requirements, and at competitive costs. If we or any of our product collaborators or third-party manufacturers, product packagers, or labelers are unable to maintain regulatory compliance, the FDA can impose regulatory sanctions, including, among other things, refusal to approve a pending application for a new drug or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition, and results of operations may be materially harmed.

If the testing or use of our products harms people, we could be subject to costly and damaging product liability claims.

The testing, manufacturing, marketing, and sale of drugs for use in people expose us to product liability risk. Any informed consent or waivers obtained from people who sign up for our clinical trials may not protect us from liability or the cost of litigation. Our product liability insurance may not cover all potential liabilities or may not completely cover any liability arising from any such litigation. Moreover, we may not have access to liability insurance or be able to maintain our insurance on acceptable terms.

Our operations may involve hazardous materials and are subject to environmental, health, and safety laws and regulations. We may incur substantial liability arising from our activities involving the use of hazardous materials.

As a biopharmaceutical company with significant manufacturing operations, we are subject to extensive environmental, health, and safety laws and regulations, including those governing the use of hazardous materials. Our research and development and manufacturing activities involve the controlled use of chemicals, viruses, radioactive compounds, and other hazardous materials. The cost of compliance with environmental, health, and safety regulations is substantial. If an accident involving these materials or an environmental discharge were to occur, we could be held liable for any resulting damages, or face regulatory actions, which could exceed our resources or insurance coverage.

Changes in the securities laws and regulations have increased, and are likely to continue to increase, our costs.

The Sarbanes-Oxley Act of 2002, which became law in July 2002, has required changes in some of our corporate governance, securities disclosure and compliance practices. In response to the requirements of that Act, the SEC and the NASDAQ Stock Market have promulgated new rules and listing standards covering a variety of subjects. Compliance with these new rules and listing standards has increased our legal costs, and significantly increased our accounting and auditing costs, and we expect these costs to continue. These developments may make it more difficult and more expensive for us to obtain directors' and officers' liability insurance. Likewise, these developments may make it more difficult for us to attract and retain qualified

members of our board of directors, particularly independent directors, or qualified executive officers.

In future years, if we or our independent registered public accounting firm are unable to conclude that our internal control over financial reporting is effective, the market value of our common stock could be adversely affected.

As directed by Section 404 of the Sarbanes-Oxley Act of 2002, the SEC adopted rules requiring public companies to include a report of management on the Company's internal control over financial reporting in their annual reports on Form 10-K that contains an assessment by management of the effectiveness of our internal control over financial reporting. In addition, the independent registered public accounting firm auditing our financial statements must attest to and report on management's assessment and on the effectiveness of our internal control over financial reporting. Our independent registered public accounting firm provided us with an unqualified report as to our assessment and the effectiveness of our internal control over financial reporting as of December 31, 2006, which report was included in our Annual Report on Form 10-K. However, we cannot assure you that management or our independent registered public accounting firm will be able to provide such an assessment or unqualified report as of future year-ends. In this event, investors could lose confidence in the reliability of our financial statements, which could result in a decrease in the market value of our common stock. In addition, if it is determined that deficiencies in the design or operation of internal controls exist and that they are reasonably likely to adversely affect our ability to record, process, summarize, and report financial information, we would likely incur additional costs to remediate these deficiencies and the costs of such remediation could be material.

Risks Related to Our Dependence on Third Parties

If our collaboration with sanofi-aventis for aflibercept (VEGF Trap) is terminated, our business operations and our ability to develop, manufacture, and commercialize aflibercept in the time expected, or at all, would be harmed.

We rely heavily on sanofi-aventis to assist with the development of the aflibercept program. Sanofi-aventis funds all of the development expenses incurred by both companies in connection with the aflibercept program. If the aflibercept program continues, we will rely on sanofi-aventis to assist with funding the aflibercept program, provide commercial manufacturing capacity, enroll and monitor clinical trials, obtain regulatory approval, particularly outside the United States, and provide sales and marketing support. While we cannot assure you that aflibercept will ever be successfully developed and commercialized, if sanofi-aventis does not perform its obligations in a timely manner, or at all, our ability to develop, manufacture, and commercialize aflibercept in cancer indications will be significantly adversely affected. Sanofi-aventis has the right to terminate its collaboration agreement with us at any time upon twelve months advance notice. If sanofi-aventis were to terminate its collaboration agreement with us, we would not have the resources or skills to replace those of our partner, which could cause significant delays in the development and/or manufacture of aflibercept and result in substantial additional costs to us. We have no sales, marketing, or distribution capabilities and would have to develop or outsource these capabilities. Termination of the sanofi-aventis collaboration agreement would create substantial new and additional risks to the successful development of the aflibercept program.

If our collaboration with Bayer HealthCare for the VEGF Trap-Eye is terminated, our business operations and our ability to develop, manufacture, and commercialize the VEGF Trap-Eye in the time expected, or at all, would be harmed.

We rely heavily on Bayer HealthCare to assist with the development of the VEGF Trap-Eye. Under our agreement with them, Bayer HealthCare is required to fund approximately half of the development expenses incurred by both companies in connection with the global VEGF Trap-Eye development program. If the VEGF Trap-Eye program continues, we will rely on Bayer HealthCare to assist with funding the VEGF Trap-Eye development program, provide assistance with the enrollment and monitoring of clinical trials conducted outside the United States, obtaining regulatory approval outside the United States, and provide sales, marketing and commercial support for the product outside the United States. In particular, Bayer HealthCare has responsibility for selling VEGF Trap-Eye outside the United States using its sales force. While we cannot assure you that the VEGF Trap-Eye will ever be successfully developed and commercialized, if Bayer HealthCare does not perform its obligations in a timely manner, or at all, our ability to develop, manufacture, and commercialize the VEGF Trap-Eye outside the United States will be significantly adversely affected. Bayer HealthCare has the right to terminate its collaboration agreement with us at any time upon six or twelve months advance notice, depending on the circumstances giving rise to termination. If Bayer HealthCare were to terminate its collaboration agreement with us, we would not have the resources or skills to replace those of our partner, which could cause significant delays in the development and/or commercialization of the VEGF Trap-Eye outside the United States and result in substantial additional costs to us. We have no sales, marketing, or distribution capabilities and would have to develop or outsource these capabilities outside the United States. Termination of the Bayer HealthCare collaboration agreement would create substantial new and additional risks to the successful development of the VEGF Trap-Eye development program.

Our collaborators and service providers may fail to perform adequately in their efforts to support the development, manufacture, and commercialization of our drug candidates.

We depend upon third-party collaborators, including sanofi-aventis, Bayer HealthCare, and service providers such as clinical research organizations, outside testing laboratories, clinical investigator sites, and third-party manufacturers and product packagers and labelers, to assist us in the development of our product candidates. If any of our existing collaborators or service providers breaches or terminates its agreement with us or does not perform its development or manufacturing services under an agreement in a timely manner or at all, we could experience additional costs, delays, and difficulties in the development or ultimate commercialization of our product candidates.

Risks Related to the Manufacture of Our Product Candidates

We have limited manufacturing capacity, which could inhibit our ability to successfully develop or commercialize our drugs.

Our manufacturing facility is likely to be inadequate to produce sufficient quantities of product for commercial sale. We intend to rely on our corporate collaborators, as well as contract manufacturers, to produce the large quantities of drug material needed for commercialization of

our products. We rely entirely on third-party manufacturers for filling and finishing services. We will have to depend on these manufacturers to deliver material on a timely basis and to comply with regulatory requirements. If we are unable to supply sufficient material on acceptable terms, or if we should encounter delays or difficulties in our relationships with our corporate collaborators or contract manufacturers, our business, financial condition, and results of operations may be materially harmed.

We may expand our own manufacturing capacity to support commercial production of active pharmaceutical ingredients, or API, for our product candidates. This will require substantial additional funds, and we will need to hire and train significant numbers of employees and managerial personnel to staff our facility. Start-up costs can be large and scale-up entails significant risks related to process development and manufacturing yields. We may be unable to develop manufacturing facilities that are sufficient to produce drug material for clinical trials or commercial use. In addition, we may be unable to secure adequate filling and finishing services to support our products. As a result, our business, financial condition, and results of operations may be materially harmed.

We may be unable to obtain key raw materials and supplies for the manufacture of our product candidates. In addition, we may face difficulties in developing or acquiring production technology and managerial personnel to manufacture sufficient quantities of our product candidates at reasonable costs and in compliance with applicable quality assurance and environmental regulations and governmental permitting requirements.

If any of our clinical programs are discontinued, we may face costs related to the unused capacity at our manufacturing facilities.

We have large-scale manufacturing operations in Rensselaer, New York. We use our facilities to produce bulk product for clinical and preclinical candidates for ourselves and our collaborations. If our clinical candidates are discontinued, we will have to absorb one hundred percent of related overhead costs and inefficiencies.

Certain of our raw materials are single-sourced from third parties; third-party supply failures could adversely affect our ability to supply our products.

Certain raw materials necessary for manufacturing and formulation of our product candidates are provided by single-source unaffiliated third-party suppliers. We would be unable to obtain these raw materials for an indeterminate period of time if these third-party single-source suppliers were to cease or interrupt production or otherwise fail to supply these materials or products to us for any reason, including due to regulatory requirements or action, due to adverse financial developments at or affecting the supplier, or due to labor shortages or disputes. This, in turn, could materially and adversely affect our ability to manufacture our product candidates for use in clinical trials, which could materially and adversely affect our business and future prospects.

Also, certain of the raw materials required in the manufacturing and the formulation of our clinical candidates may be derived from biological sources, including mammalian tissues, bovine serum, and human serum albumin. There are certain European regulatory restrictions on using these biological source materials. If we are required to substitute for these sources to comply

with European regulatory requirements, our clinical development activities may be delayed or interrupted.

Risks Related to Commercialization of Products

If we are unable to establish sales, marketing, and distribution capabilities, or enter into agreements with third parties to do so, we will be unable to successfully market and sell future products.

We have no sales or distribution personnel or capabilities and have only a small staff with marketing capabilities. If we are unable to obtain those capabilities, either by developing our own organizations or entering into agreements with service providers, we will not be able to successfully sell any products that we may obtain regulatory approval for and bring to market in the future. In that event, we will not be able to generate significant revenue, even if our product candidates are approved. We cannot guarantee that we will be able to hire the qualified sales and marketing personnel we need or that we will be able to enter into marketing or distribution agreements with third-party providers on acceptable terms, if at all. Under the terms of our collaboration agreement with sanofi-aventis, we currently rely on sanofi-aventis for sales, marketing, and distribution of aflibercept in cancer indications, should it be approved in the future by regulatory authorities for marketing. We will have to rely on a third party or devote significant resources to develop our own sales, marketing, and distribution capabilities for our other product candidates, including the VEGF Trap-Eye in the United States, and we may be unsuccessful in developing our own sales, marketing, and distribution organization.

Even if our product candidates are approved for marketing, their commercial success is highly uncertain because our competitors have received approval for products with the same mechanism of action, and competitors may get to the marketplace before we do with better or lower cost drugs or the market for our product candidates may be too small to support commercialization or sufficient profitability.

There is substantial competition in the biotechnology and pharmaceutical industries from pharmaceutical, biotechnology, and chemical companies. Many of our competitors have substantially greater research, preclinical and clinical product development and manufacturing capabilities, and financial, marketing, and human resources than we do. Our smaller competitors may also enhance their competitive position if they acquire or discover patentable inventions, form collaborative arrangements, or merge with large pharmaceutical companies. Even if we achieve product commercialization, our competitors have achieved, and may continue to achieve, product commercialization before our products are approved for marketing and sale.

Genentech has an approved VEGF antagonist, Avastin ® (Genentech), on the market for treating certain cancers and many different pharmaceutical and biotechnology companies are working to develop competing VEGF antagonists, including Novartis, OSI Pharmaceuticals, and Pfizer. Many of these molecules are farther along in development than aflibercept and may offer competitive advantages over our molecule . Novartis has an ongoing Phase 3 clinical development program evaluating an orally delivered VEGF tyrosine kinase inhibitor in different cancer settings. Each of Pfizer and Onyx Pharmaceuticals (together with its partner Bayer HealthCare) has received approval from the FDA to market and sell an oral medication that targets tumor cell growth and new vasculature formation that fuels the growth of tumors. The

marketing approvals for Genentech's VEGF antagonist, Avastin ® (Genentech), and their extensive, ongoing clinical development plan for Avastin ® (Genentech) in other cancer indications, may make it more difficult for us to enroll patients in clinical trials to support aflibercept and to obtain regulatory approval of aflibercept in these cancer settings. This may delay or impair our ability to successfully develop and commercialize aflibercept. In addition, even if aflibercept is ever approved for sale for the treatment of certain cancers, it will be difficult for our drug to compete against Avastin ® (Genentech) and the FDA approved kinase inhibitors, because doctors and patients will have significant experience using these medicines. In addition, an oral medication may be considerably less expensive for patients than a biologic medication, providing a competitive advantage to companies that market such products.

The market for eye disease products is also very competitive. Novartis and Genentech are collaborating on the commercialization and further development of a VEGF antibody fragment (Lucentis ®) for the treatment of age-related macular degeneration (wet AMD) and other eye indications that was approved by the FDA in June 2006. OSI Pharmaceuticals and Pfizer are marketing an approved VEGF inhibitor for wet AMD. Many other companies are working on the development of product candidates for the potential treatment of wet AMD that act by blocking VEGF, VEGF receptors, and through the use of soluble ribonucleic acids (sRNAs) that modulate gene expression. In addition, ophthalmologists are using off-label a third-party reformatted version of Genentech's approved VEGF antagonist, Avastin ® , with success for the treatment of wet AMD. The National Eye Institute recently has received funding for a Phase 3 trial to compare Lucentis ® (Genentech) to Avastin ® (Genentech) in the treatment of wet AMD. The marketing approval of Lucentis ® (Genentech) and the potential off-label use of Avastin ® (Genentech) make it more difficult for us to enroll patients in our clinical trials and successfully develop the VEGF Trap-Eye. Even if the VEGF Trap-Eye is ever approved for sale for the treatment of eye diseases, it may be difficult for our drug to compete against Lucentis ® (Genentech), because doctors and patients will have significant experience using this medicine. Moreover, the relatively low cost of therapy with Avastin ® (Genentech) in patients with wet AMD presents a further competitive challenge in this indication.

The availability of highly effective FDA approved TNF-antagonists such as Enbrel ® (Immunex), Remicade ® (Centocor), and Humira ® (Abbott Biotechnology Ltd.), and the IL-1 receptor antagonist Kineret ® (Amgen), and other marketed therapies makes it more difficult to successfully develop and commercialize rilonacept. This is one of the reasons we discontinued the development of rilonacept in adult rheumatoid arthritis. In addition, even if rilonacept is ever approved for sale, it will be difficult for our drug to compete against these FDA approved TNF-antagonists in indications where both are useful because doctors and patients will have significant experience using these effective medicines. Moreover, in such indications these approved therapeutics may offer competitive advantages over rilonacept, such as requiring fewer injections.

There are both small molecules and antibodies in development by third parties that are designed to block the synthesis of interleukin-1 or inhibit the signaling of interleukin-1. For example, Eli Lilly and Company and Novartis are each developing antibodies to interleukin-1 and Amgen is developing an antibody to the interleukin-1 receptor. It has been reported that Novartis has commenced advanced clinical testing of its IL-1 antibody in Muckle-Wells Syndrome, which is part of the group of rare genetic diseases called CAPS. Novartis' IL-1 antibody and these other drug candidates could offer competitive advantages over rilonacept.

The successful development of these competing molecules could delay or impair our ability to successfully develop and commercialize rilonacept. For example, we may find it difficult to enroll patients in clinical trials for rilonacept if the companies developing these competing interleukin-1 inhibitors commence clinical trials in the same indications.

We are developing rilonacept for the treatment of a group of rare diseases associated with mutations in the *CIAS* 1 gene. These rare genetic disorders affect a small group of people, estimated to be between several hundred and a few thousand. There may be too few patients with these genetic disorders to profitably commercialize rilonacept in this indication.

The successful commercialization of our product candidates will depend on obtaining coverage and reimbursement for use of these products from third-party payers and these payers may not agree to cover or reimburse for use of our products.

Our products, if commercialized, may be significantly more expensive than traditional drug treatments. Our future revenues and profitability will be adversely affected if United States and foreign governmental, private third-party insurers and payers, and other third-party payers, including Medicare and Medicaid, do not agree to defray or reimburse the cost of our products to the patients. If these entities refuse to provide coverage and reimbursement with respect to our products or provide an insufficient level of coverage and reimbursement, our products may be too costly for many patients to afford them, and physicians may not prescribe them. Many third-party payers cover only selected drugs, making drugs that are not preferred by such payer more expensive for patients, and require prior authorization or failure on another type of treatment before covering a particular drug. Payers may especially impose these obstacles to coverage on higher-priced drugs, as our product candidates are likely to be.

We are seeking approval to market rilonacept for the treatment of a group of rare genetic disorders called CAPS. There may be too few patients with CAPS to profitably commercialize rilonacept. Physicians may not prescribe rilonacept and CAPS patients may not be able to afford rilonacept if third party payers do not agree to reimburse the cost of rilonacept therapy and this would adversely affect our ability to commercialize rilonacept profitably.

In addition to potential restrictions on coverage, the amount of reimbursement for our products may also reduce our profitability. In the United States, there have been, and we expect will continue to be, actions and proposals to control and reduce healthcare costs. Government and other third-party payers are challenging the prices charged for healthcare products and increasingly limiting, and attempting to limit, both coverage and level of reimbursement for prescription drugs.

Since our products, including rilonacept, will likely be too expensive for most patients to afford without health insurance coverage, if our products are unable to obtain adequate coverage and reimbursement by third-party payers our ability to successfully commercialize our product candidates may be adversely impacted. Any limitation on the use of our products or any decrease in the price of our products will have a material adverse effect on our ability to achieve profitability.

In certain foreign countries, pricing, coverage and level of reimbursement of prescription drugs are subject to governmental control, and we may be unable to negotiate coverage, pricing,

and reimbursement on terms that are favorable to us. In some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Our results of operations may suffer if we are unable to market our products in foreign countries or if coverage and reimbursement for our products in foreign countries is limited.

Risk Related to Employees

We are dependent on our key personnel and if we cannot recruit and retain leaders in our research, development, manufacturing, and commercial organizations, our business will be harmed.

We are highly dependent on certain of our executive officers. If we are not able to retain any of these persons or our Chairman, our business may suffer. In particular, we depend on the services of P. Roy Vagelos, M.D., the Chairman of our board of directors, Leonard Schleifer, M.D., Ph.D., our President and Chief Executive Officer, George D. Yancopoulos, M.D., Ph.D., our Executive Vice President, Chief Scientific Officer and President, Regeneron Research Laboratories, and Neil Stahl, Ph.D., our Senior Vice President, Research and Development Sciences. There is intense competition in the biotechnology industry for qualified scientists and managerial personnel in the development, manufacture, and commercialization of drugs. We may not be able to continue to attract and retain the qualified personnel necessary for developing our business.

Risks Related to Our Common Stock

Our stock price is extremely volatile.

There has been significant volatility in our stock price and generally in the market prices of biotechnology companies' securities. Various factors and events may have a significant impact on the market price of our common stock. These factors include, by way of example:

- progress, delays, or adverse results in clinical trials;
- announcement of technological innovations or product candidates by us or competitors;
- fluctuations in our operating results;
- public concern as to the safety or effectiveness of our product candidates;
- developments in our relationship with collaborative partners;
- developments in the biotechnology industry or in government regulation of healthcare;
- large sales of our common stock by our executive officers, directors, or significant shareholders;
- arrivals and departures of key personnel; and
- general market conditions.

The trading price of our common stock has been, and could continue to be, subject to wide fluctuations in response to these and other factors, including the sale or attempted sale of a large amount of our common stock in the market. Broad market fluctuations may also adversely affect the market price of our common stock.

Future sales of our common stock by our significant shareholders or us may depress our stock price and impair our ability to raise funds in new share offerings.

A small number of our shareholders beneficially own a substantial amount of our common stock. As of September 30, 2007, our seven largest shareholders beneficially owned 42.3% of our outstanding shares of Common Stock, assuming, in the case of Leonard S. Schleifer, M.D. Ph.D., our Chief Executive Officer, and P. Roy Vagelos, M.D., our Chairman, the conversion of their Class A Stock into Common Stock and the exercise of all options held by them which are exercisable within 60 days of September 30, 2007. As of September 30, 2007, sanofi-aventis owned 2,799,552 shares of Common Stock, representing approximately 4.4% of the shares of Common Stock then outstanding. Under our stock purchase agreement with sanofi-aventis, sanofi-aventis may sell no more than 500,000 of these shares in any calendar quarter. If sanofi-aventis, or our other significant shareholders or we, sell substantial amounts of our Common Stock in the public market, or the perception that such sales may occur exists, the market price of our Common Stock could fall. Sales of Common Stock by our significant shareholders, including sanofi-aventis, also might make it more difficult for us to raise funds by selling equity or equity-related securities in the future at a time and price that we deem appropriate.

Our existing shareholders may be able to exert significant influence over matters requiring shareholder approval.

Holders of Class A Stock, who are generally the shareholders who purchased their stock from us before our initial public offering, are entitled to ten votes per share, while holders of Common Stock are entitled to one vote per share. As of September 30, 2007, holders of Class A Stock held 26.2% of the combined voting power of all of Common Stock and Class A Stock then outstanding. These shareholders, if acting together, would be in a position to significantly influence the election of our directors and to effect or prevent certain corporate transactions that require majority or supermajority approval of the combined classes, including mergers and other business combinations. This may result in our company taking corporate actions that you may not consider to be in your best interest and may affect the price of our Common Stock. As of September 30, 2007:

- our current executive officers and directors beneficially owned 12.9% of our outstanding shares of Common Stock, assuming conversion of their Class A Stock into Common Stock and the exercise of all options held by such persons which are exercisable within 60 days of September 30, 2007, and 30.2% of the combined voting power of our outstanding shares of Common Stock and Class A Stock, assuming the exercise of all options held by such persons which are exercisable within 60 days of September 30, 2007; and
- our seven largest shareholders beneficially owned 42.3% of our outstanding shares of Common Stock, assuming, in the case of Leonard S. Schleifer, M.D., Ph.D., our Chief Executive Officer, and P. Roy Vagelos, M.D., our Chairman, the conversion of their

Class A Stock into Common Stock and the exercise of all options held by them which are exercisable within 60 days of September 30, 2007. In addition, these seven shareholders held 49.6% of the combined voting power of our outstanding shares of Common Stock and Class A Stock, assuming the exercise of all options held by our Chief Executive Officer and our Chairman which are exercisable within 60 days of September 30, 2007.

The anti-takeover effects of provisions of our charter, by-laws, and of New York corporate law, could deter, delay, or prevent an acquisition or other "change in control" of us and could adversely affect the price of our common stock.

Our amended and restated certificate of incorporation, our by-laws and the New York Business Corporation Law contain various provisions that could have the effect of delaying or preventing a change in control of our company or our management that shareholders may consider favorable or beneficial. Some of these provisions could discourage proxy contests and make it more difficult for you and other shareholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions include:

- authorization to issue "blank check" preferred stock, which is preferred stock that can be created and issued by the board of directors without prior shareholder approval, with rights senior to those of our common shareholders;
- a staggered board of directors, so that it would take three successive annual meetings to replace all of our directors;
- a requirement that removal of directors may only be effected for cause and only upon the affirmative vote of at least eighty percent (80%) of the outstanding shares entitled to vote for directors, as well as a requirement that any vacancy on the board of directors may be filled only by the remaining directors;
- any action required or permitted to be taken at any meeting of shareholders may be taken without a meeting, only if, prior to such action, all of our shareholders consent, the effect of which is to require that shareholder action may only be taken at a duly convened meeting;
- any shareholder seeking to bring business before an annual meeting of shareholders must provide timely notice of this intention in writing and meet various other requirements; and
- under the New York Business Corporation Law, a plan of merger or consolidation of the Company must be approved by two-thirds of the votes of all outstanding shares entitled to vote thereon. See the risk factor immediately above captioned *"Our existing shareholders may be able to exert significant influence over matters requiring shareholder approval."*

In addition, we have a Change in Control Severance Plan and our chief executive officer has an employment agreement that provides severance benefits in the event our officers are terminated as a result of a change in control of the Company. Many of our stock options issued under our 2000 Long-Term Incentive Plan may become fully vested in connection with a "change in control" of our company, as defined in the plan.

Item 6. Exhibits

(a) Exhibits

Exhibit Number	Description
10.1*	- First Amendment to Lease, by and between BMR-Landmark at Eastview LLC and Regeneron Pharmaceuticals, Inc., effective as of October 24, 2007.
12.1	- Statement re: computation of ratio of earnings to combined fixed charges.
31.1	- Certification of CEO pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934.
31.2	- Certification of CFO pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934.
32	- Certification of CEO and CFO pursuant to 18 U.S.C. Section 1350.

* Portions of this document have been omitted and filed separately with the Commission pursuant to requests for confidential treatment pursuant to Rule 24b-2.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Regeneron Pharmaceuticals, Inc.

Date: November 7, 2007

By: /s/ Murray A. Goldberg
Murray A. Goldberg
Senior Vice President, Finance & Administration,
Chief Financial Officer, Treasurer, and
Assistant Secretary
(Principal Financial Officer and
Duly Authorized Officer)

Exhibit 10.1

* Confidential Materials Omitted And Filed Separately With The Securities And Exchange Commission. Asterisks Denote Omissions.

FIRST AMENDMENT TO LEASE

This **First Amendment to Lease** (this " **Amendment** ") is entered into as of September 14, 2007 (the " **First Amendment Date** ") by and between BMR-Landmark at Eastview LLC, a Delaware limited liability company (" **Landlord** "), and Regeneron Pharmaceuticals, Inc., a New York corporation (" **Tenant** ").

RECITALS

(A) Landlord and Tenant are parties to that certain Lease (the " **Lease** ") dated as of December 21, 2006, pursuant to which Landlord (a) leases the Premises (as defined in the Lease) to Tenant and (b) has provided Tenant an option (the " **Expansion Option** ") to expand the Premises and take occupancy of the entire New Multiple Tenant Building. All capitalized terms used but not otherwise defined herein shall have the meanings given such terms in the Lease.

(B) Tenant has delivered to Landlord the Expansion Notice.

(C) Landlord and Tenant desire to amend certain terms of the Lease, as set forth below, to reflect their understanding with respect to such terms and the addition of the Expansion Space (as defined below) to the Premises.

AGREEMENT

NOW, THEREFORE, Landlord and Tenant, in consideration of the mutual promises contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, agree as follows:

A. Amendments

1. Expansion Space . The Lease is hereby amended to include the first floor of the New Multiple Tenant Building, as depicted on Exhibit A attached to the Lease (the " **Expansion Space** "), so that such space constitutes a part of, and is included within the meaning of, the "New Multiple Tenant Building Premises", the "New Premises" and the "Premises", as such terms are used in the Lease. The Expansion Space shall be delivered to Tenant together with the rest of the New Multiple Tenant Building Premises in accordance with the terms of the Lease, so that the entire New Multiple Tenant Building will be leased to Tenant. Except as specifically provided otherwise herein or in the Lease, all of the terms and conditions set forth herein and in the Lease shall apply to the Expansion Space. The description of the Expansion Space set forth on Exhibit A attached hereto is hereby added to the description of the New Multiple Tenant Building Premises on Exhibit A to the Lease. The mere exercise by Tenant of the Expansion Option and any additional Landlord Work required to be performed to deliver possession of the Expansion Premises in the condition and on the date provided in the Lease, shall not constitute a Tenant Delay under this Lease.

2. Estimated Term Commencement Date . Section 2.6 of the Lease is hereby amended by replacing the date "March 6, 2008" where such date appears therein with the date "June 20, 2008".

3. Exhibit F. Exhibit F to the Lease is hereby amended by (i) replacing the value "$68,107,092", where such value appears in the letter therein, dated December 12, 2006, from David Surette to Steve Marshall, with the value "68,159,687" and (ii) replacing the Schedule of Values therein with the Schedule of Values attached hereto as Exhibit B.

B. Miscellaneous

1. This Amendment shall be governed by, construed and enforced in accordance with the laws of the state in which the Premises are located, without regard to such state's conflict of law principles.

2. Tenant and Landlord each represents and warrants to the other that it has had no dealings with any real estate broker or agent in connection with the negotiation of this Amendment other than Studley, Inc. ("Broker"), and that it knows of no other real estate broker or agent that is or might be entitled to a commission in connection with this Amendment. Landlord shall compensate Broker in relation to this Amendment pursuant to a separate agreement between Landlord and Broker

3. Each of Landlord and Tenant represents that, except as amended hereby, the Lease has not been modified and remains in full force and effect and the individual or those individuals signing this Amendment on behalf of Landlord or Tenant (respectively) have the power, authority and legal capacity to sign this Amendment on behalf of and to bind all entities, corporations, partnerships, limited liability companies, joint venturers or other organizations and entities on whose behalf said individual or individuals have signed.

4. This Amendment may be executed in one or more counterparts, each of which, when taken together, shall constitute one and the same document.

Remainder of Page Intentionally Left Blank.
Signature Page Follows.

IN WITNESS WHEREOF, the parties hereto have executed this Amendment as of the date first above written.

LANDLORD:

BMR-Landmark at Eastview LLC,
a Delaware limited liability company

By: /s/ Matthew G. McDevitt
Name: Matthew G. McDevitt
Title: Regional Executive Vice President

TENANT:

Regeneron Pharmaceuticals, Inc.,
a New York corporation

By: /s/ Murray A. Goldberg
Name: Murray A. Goldberg
Title: Senior Vice President, Finance & Administration and Chief Financial Officer

EXHIBIT A

EXPANSION SPACE

EXHIBIT A

EXPANSION SPACE DESCRIPTION

The Expansion Space is the entire first floor of the New Multiple Tenant Building, along with the remaining portions of the basement and penthouse. The Rentable Area of the Expansion Space shall be defined as follows:

First floor= 33,169 square feet
Basement= 1,738 square feet
Penthouse= 849 square feet
Total Rentable Area of Expansion Space= 35,756 square feet*

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* The Lease incorrectly references total Rentable Area of Expansion Space as 35,755 square feet.

EXHIBIT B

SCHEDULE OF VALUES

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Exhibit 12.1

Regeneron Pharmaceuticals, Inc.
Computation of Ratio of Earnings to Combined Fixed Charges
(Dollars in thousands)

	Years ended December 31,					Nine months ended September 30,
	2002	2003	2004	2005	2006	2007
Earnings:						
Income (loss) from continuing operations before income (loss) from equity investee	$(124,350)	$(107,395)	$41,565	$(95,456)	$(103,150)	$ (92,529)
Fixed charges	13,685	14,108	14,060	13,687	13,643	10,285
Amortization of capitalized interest	—	33	78	78	73	18
Interest capitalized	(222)	(276)	—	—	—	—
Adjusted earnings	$(110,887)	$ (93,530)	$55,703	$(81,691)	$ (89,434)	$ (82,226)
Fixed charges:						
Interest expense	$ 11,859	$ 11,932	$12,175	$ 12,046	$ 12,043	$ 9,033
Interest capitalized	222	276	—	—	—	—
Assumed interest component of rental charges	1,604	1,900	1,885	1,641	1,600	1,252
Total fixed charges	$ 13,685	$ 14,108	$14,060	$ 13,687	$ 13,643	$ 10,285
Ratio of earnings to fixed charges	(A)	(A)	3.96	(A)	(A)	(A)

(A) Due to the registrant's losses for the years ended December 31, 2002, 2003, 2005, and 2006, and for the nine months ended September 30, 2007, the ratio coverage was less than 1:1. To achieve a coverage ratio of 1:1, the registrant must generate additional earnings of the amounts shown in the table below.

	Years ended December 31,				Nine months ended September 30,
	2002	2003	2005	2006	2007
Coverage deficiency	$124,572	$107,638	$95,378	$103,077	$92,511

Exhibit 31.1

Certification of CEO Pursuant to
Rule 13a-14(a) under the Securities Exchange Act
of 1934, as Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Leonard S. Schleifer, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Regeneron Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations, and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2007

/s/ Leonard S. Schleifer
Leonard S. Schleifer, M.D., Ph.D.
President and Chief Executive Officer

Exhibit 31.2

Certification of CFO Pursuant to
Rule 13a-14(a) under the Securities Exchange Act
of 1934, as Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Murray A. Goldberg, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Regeneron Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations, and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2007

/s/ Murray A. Goldberg
Murray A. Goldberg
Senior Vice President, Finance &
Administration, Chief Financial Officer,
Treasurer, and Assistant Secretary

Exhibit 32

Certification of CEO and CFO Pursuant to
18 U.S.C. Section 1350,
As Adopted Pursuant to
Section 906 of the Sarbanes-Oxley Act of 2002

In connection with the Quarterly Report of Regeneron Pharmaceuticals, Inc. (the "Company") on Form 10-Q for the quarterly period ended September 30, 2007 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Leonard S. Schleifer, M.D., Ph.D., as Chief Executive Officer of the Company, and Murray A. Goldberg, as Chief Financial Officer of the Company, each hereby certifies, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, to the best of his knowledge, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Leonard S. Schleifer
Leonard S. Schleifer, M.D., Ph.D.
Chief Executive Officer
November 7, 2007

/s/ Murray A. Goldberg
Murray A. Goldberg
Chief Financial Officer
November 7, 2007

OBS 8

REGENERON
science to medicine®

May 1, 2008

Regeneron Reports First Quarter 2008 Financial and Operating Results

TARRYTOWN, N.Y., May 01, 2008 (BUSINESS WIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced financial and operating results for the first quarter 2008. The Company reported a net loss of $11.6 million, or $0.15 per share (basic and diluted), for the first quarter of 2008 compared with a net loss of $29.9 million, or $0.46 per share (basic and diluted), for the first quarter of 2007.

At March 31, 2008, cash, restricted cash, and marketable securities totaled $827.9 million compared with $846.3 million at December 31, 2007. The Company's $200.0 million of convertible notes, which bear interest at 5.5 percent per annum, mature in October 2008.

Current Business Highlights

ARCALYST™ (rilonacept) - Inflammatory Diseases

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

A Phase 2 safety and efficacy trial of ARCALYST is underway in the prevention of gout flares induced by the initiation of uric acid-lowering drug therapy used to control gout. The Company is also evaluating the potential use of ARCALYST in other indications in which interleukin-1 (IL-1) may play a role.

Aflibercept (VEGF Trap) - Oncology

In their collaboration to develop aflibercept for the treatment of cancer, Regeneron and sanofi-aventis currently are enrolling patients in four Phase 3 trials that combine aflibercept with standard chemotherapy regimens. One trial is evaluating aflibercept as a 2nd line treatment for metastatic colorectal cancer in combination with folinic acid, 5-FU, and irinotecan. A second trial is evaluating aflibercept as a 1st line treatment for metastatic pancreatic cancer in combination with gemcitabine. A third trial is evaluating aflibercept as a 1st line treatment for metastatic androgen independent prostate cancer in combination with docetaxel/prednisone. The fourth trial is evaluating aflibercept as a 2nd line treatment for metastatic non-small cell lung cancer in combination with docetaxel. All four trials are studying the current standard of chemotherapy care for the cancer being studied with and without aflibercept. In addition, more than 13 studies are being conducted in conjunction with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) evaluating aflibercept as a single agent or in combination with chemotherapy regimens in a variety of cancer indications.

VEGF Trap-Eye - Eye Diseases

VEGF Trap-Eye is a specially purified and formulated form of the VEGF Trap for use in intraocular applications. Regeneron and Bayer HealthCare initiated a Phase 3 global development program of VEGF Trap-Eye in the neovascular form of Age-related Macular Degeneration (wet AMD) in the third quarter of 2007. The first trial, known as VIEW 1 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), is comparing VEGF Trap-Eye and ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.), an anti-angiogenic agent approved for use in wet AMD. The trial is evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye, compared with ranibizumab dosed every four weeks according to its label. Bayer HealthCare is initiating a second Phase 3 trial of VEGF Trap-Eye in wet AMD in the European Union and other parts of the world outside the U.S.

In April 2008, Regeneron and Bayer HealthCare announced the 32-week endpoint results of a Phase 2 study evaluating VEGF Trap-Eye in wet AMD, which were presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, Florida. The analysis showed that VEGF Trap-Eye dosed on a PRN (as-needed) dosing schedule maintained the statistically significant gain in visual acuity achieved after an initial 12-week, fixed-dosing phase.

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

Patients receiving monthly doses of VEGF Trap-Eye, either 0.5 or 2.0 mg, for 12 weeks followed by PRN dosing thereafter achieved mean improvements in visual acuity of 8.0 (p less than0.01 versus baseline) and 10.1 letters (p less than 0.0001 versus baseline), respectively, and mean decreases in retinal thickness of 141 (p less than 0.0001 versus baseline) and 162 microns (p less than 0.0001 versus baseline) at week 32, respectively.

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

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

Monoclonal Antibodies

Regeneron and sanofi-aventis are collaborating on the discovery, development, and commercialization of fully human monoclonal antibodies generated by Regeneron using its VelocImmune® technology. The first therapeutic antibody to enter clinical development under the collaboration is REGN88, an antibody to the interleukin-6 receptor (IL-6R) that is being evaluated in rheumatoid arthritis. A second antibody candidate, an antibody to Delta-like ligand-4 (Dll4), is slated to start clinical development in mid-2008. The Company and sanofi-aventis plan to advance two to three new antibodies into clinical development each year.

Financial Results

Revenue

Regeneron's total revenue increased to $56.4 million in the first quarter of 2008 from $15.8 million in the same period of 2007. Contract research and development revenue in the first quarter of 2008 principally related to the Company's aflibercept and antibody collaborations with sanofi-aventis and the Company's VEGF Trap-Eye collaboration with Bayer HealthCare. In the first quarter of 2007, contract research and development revenue primarily related to the Company's aflibercept collaboration with sanofi-aventis. Technology licensing revenue related to the Company's license agreements with AstraZeneca and Astellas.

Regeneron recognized contract research and development revenue of $13.8 million in the first quarter of 2008 related to the Company's aflibercept collaboration with sanofi-aventis, compared with $11.8 million in the same period of 2007. Contract research and development revenue from the collaboration consisted of reimbursement of aflibercept development expenses incurred by the Company plus recognition of amounts related to $105.0 million of previously received and deferred non-refundable, up-front payments. Reimbursement of expenses increased to $11.7 million in the first quarter of 2008 from $9.6 million in the same period of 2007, principally due to higher costs related to the Company's manufacture of aflibercept clinical supplies and higher clinical development costs. With respect to the $105.0 million of up-front payments from sanofi-aventis, $2.1 million was recognized in the first quarter of 2008 compared to $2.2 million in the same period of 2007.

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

Regeneron recognized contract research and development revenue of $21.9 million in the first quarter of 2008 related to the Company's antibody collaboration with sanofi-aventis. Contract research and development revenue from the antibody collaboration consisted of $15.1 million for reimbursement of the Company's expenses under the collaboration's discovery agreement, $4.2 million for reimbursement of the Company's REGN88 development expenses, and $2.6 million related to an $85.0 million non-refundable, up-front payment, which was deferred upon receipt in December 2007.

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

In the first quarter of 2008, the Company recorded $9.0 million of contract research and development revenue from Bayer HealthCare, consisting of $3.3 million related to the $75.0 million up-front licensing payment and the $20.0 million milestone payment and $5.7 million related to the portion of the Company's first quarter 2008 VEGF Trap-Eye development expenses that is reimbursable from Bayer HealthCare.

Regeneron has entered into non-exclusive license agreements with AstraZeneca and Astellas that allow those companies to utilize VelocImmune® technology in their internal research programs to discover human monoclonal antibodies. Each company made a $20.0 million up-front, non-refundable payment in 2007 and will make up to five additional annual payments of $20.0 million, subject to the ability to terminate their agreements after making three additional payments. Upon receipt, these payments are deferred and are recognized as revenue ratably over approximately the ensuing year of each agreement. Regeneron will also receive a mid-single-digit royalty on sales of any antibodies discovered utilizing VelocImmune. In the first quarter of 2008 and 2007, the Company recognized $10.0 million and $2.1 million, respectively, of technology licensing revenue related to these agreements.

ARCALYST™ (rilonacept) Product Sales

In late March 2008, the Company shipped $0.8 million of ARCALYST to its distributors, which was fully deferred at March 31, 2008 and classified as deferred revenue in the Company's financial statements.

Expenses

Total operating expenses for the first quarter of 2008 were $72.3 million, 46 percent higher than the same period in 2007. Our average headcount increased to 714 in the first quarter of 2008 from 585 in the same period of 2007 primarily as a result of our expanding research and development activities directed toward preclinical and clinical development of product candidates, including ARCALYST™, aflibercept, VEGF Trap-Eye, and monoclonal antibodies (including REGN88 and the Dll4 antibody).

Operating expenses included non-cash compensation expense related to employee stock option and restricted stock awards of $8.3 million and $6.6 million in the first quarters of 2008 and 2007, respectively.

Research and development (R&D) expenses increased to $61.3 million in the first quarter of 2008 from $41.2 million in the comparable quarter of 2007. The Company incurred higher R&D costs primarily related to additional R&D headcount, clinical development costs for VEGF Trap-Eye and ARCALYST, and costs related to manufacturing supplies of aflibercept, VEGF Trap-Eye, and the Dll4 antibody.

Selling, general, and administrative expenses increased to $11.0 million in the first quarter of 2008 from $8.2 million in the comparable period of 2007. In the first quarter of 2008, the Company incurred costs associated with the launch of ARCALYST. In addition, the Company incurred higher compensation expense and recruitment costs associated with expanding the Company's headcount, and higher legal fees related to general corporate matters.

Other Income

Investment income increased to $7.3 million in the first quarter of 2008 from $6.7 million in the comparable quarter of 2007. The increase in investment income resulted primarily from higher balances of cash and marketable securities, due primarily to receipts from sanofi-aventis of $312.0 million for the purchase of 12 million shares of the Company's Common Stock in December 2007 and the $85.0 million up-front payment related to the antibody collaboration, partially offset by lower effective interest rates in 2008.

About Regeneron Pharmaceuticals

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

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

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

	March 31, 2008	December 31, 2007
ASSETS		
Cash, restricted cash, and marketable securities	$827,858	$846,279
Receivables	32,960	18,320
Property, plant, and equipment, net	58,419	58,304
Other assets	11,639	13,355
Total assets	$930,876	$936,258
LIABILITIES AND STOCKHOLDERS' EQUITY		
Accounts payable and accrued expenses	$30,314	$39,232
Deferred revenue	239,959	236,759
Notes payable	200,000	200,000
Stockholders' equity	460,603	460,267
Total liabilities and stockholders' equity	$930,876	$936,258

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

	For the three months ended March 31, 2008	2007
Revenues		
Contract research and development	$46,383	$13,645

Technology licensing	10,000	2,143
	56,383	15,788
Expenses		
Research and development	61,270	41,235
Selling, general, and administrative	11,024	8,202
	72,294	49,437
Loss from operations	(15,911)	(33,649)
Other income (expense)		
Investment income	7,304	6,743
Interest expense	(3,011)	(3,011)
	4,293	3,732
Net loss	$(11,618)	$(29,917)
Net loss per share amounts, basic and diluted	$(0.15)	$(0.46)
Weighted average shares outstanding, basic and diluted	78,493	65,563

SOURCE: Regeneron Pharmaceuticals, Inc.

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OBS4

International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–91) and Recommended (1–52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–91) et recommandées (1–52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del "Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas", se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–91) y Recomendadas (1–52) se encuentran reunidas en *Cumulative List No. 11, 2004* (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

Proposed International Nonproprietary Names: List 95

Publication date: 21 August 2006
Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List** 95 **Proposed INN not later than** 21 December 2006.

Dénominations communes internationales proposées: Liste 95

Date de publication:21 août 2006.
Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la **Liste** 95 **de DCI Proposées le** 21 décembre 2006 **au plus tard.**

Denominaciones Comunes Internacionales Propuestas: Lista 95

Fecha de la publicación: el 21 de agosto de 2006
Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para **la Lista** 95 **de DCI Propuestas el** 21 de diciembre de 2006 **a más tardar.**

Proposed INN (Latin, English, French, Spanish)	*Chemical name or description: Action and use: Molecular formula Chemical Abstracts Service (CAS) registry number: Graphic formula*
DCI Proposée	*Nom chimique ou description: Propriétés et indications: Formule brute Numéro dans le registre du CAS: Formule développée*
DCI Propuesta	*Nombre químico o descripción: Acción y uso: Fórmula molecular Número de registro del CAS: Fórmula desarrollada*

abagovomabum*	
abagovomab	immunoglobulin G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) *Mus musculus* monoclonal antibody OC125] *Mus musculus* monoclonal antibody ACA125, clone 3D5 gamma1 heavy chain disulfide with clone 3D5 kappa light chain; (223-223":226-226":228-228") trisdisulfide dimer *immunological agent, antineoplastic*
abagovomab	immunoglobuline G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) anticorps monoclonal murin OC125] anticorps monoclonal murin ACA125, chaîne lourde gamma1 du clone 3D5 unie par un pont disulfure à la chaîne légère kappa du clone 3D5; dimère (223-223":226-226":228-228")-trisdisulfure *agent immunologique, antinéoplasique*
abagovomab	inmunoglobulina G1, anti-idiotipo anti-[anti-(*Homo sapiens* cancer antígeno 125, CA 125, MUC-16) anticuerpo monoclonal murino OC125] anticuerpo monoclonal murino ACA125, cadena pesada gamma1 del clon 3D5 unida por un puente disulfuro a la cadena ligera kappa del clon 3D5; dímero (223-223":226-226":228-228")-trisdisulfuro *agente inmunológico, antineoplásico*

792921-10-9

Heavy chain/Chaîne lourde/Cadena pesada

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QVKLQESGAE LARPGASVKL SCKASGYTFT NYWMQWVKQR PGQGLDWIGA  50
IYPGDGNTRY THKFKGKATL TADKSSSTAY MQLSSLASED SGVYYCARGE 100
GNYAWFAYWG QGTTVTVSSA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG 150
YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT 200
CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT 250
LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS 300
ELPIMHQDWL NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP 350
KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY 400
FVYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK         443
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Light chain/Chaîne légère/Cadena ligera

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DIELTQSPAS LSASVGETVT ITCQASENIY SYLAWHQQKQ GKSPQLLVYN  50
AKTLAGGVSS RFSGSGSGTH FSLKIKSLQP EDFGIYYCQH HYGILPTFGG 100
GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI 150
DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT 200
STSPIVKSFN RNEC                                        214
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acidum iodofilticum (^{123}I)
iodofiltic acid (^{123}I)

(3*RS*)-15-[4-[^{123}I]iodophenyl]3-methylpentadecanoic acid
radiopharmaceutical

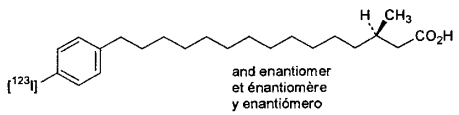
acide iodofiltique (^{123}I)

acide (3*RS*)-15-(4-[^{123}I]iodophényl)-3-méthylpentadécanoïque
radiopharmaceutique

ácido iodofiltico (^{123}I)

ácido (3*RS*)-15-(4-[^{123}I]iodofenil)-3-metilpentadecanoico
preparacion farmaceutica radiactiva

$C_{22}H_{35}{}^{123}IO_2$ 123748-56-1



aclidinii bromidum
aclidinium bromide

(3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide
muscarinic receptor antagonist

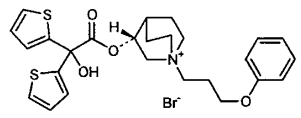
bromure d'aclidinium

bromure de (3*R*)-3-[[hydroxybis(thiophén-2-yl)acétyl]oxy]-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane
antagoniste des récepteurs muscariniques

bromuro de aclidinio

bromuro de (3R)-1-(3-fenoxipropil)-3-[(hidroxi)di(tiofen-2-il)acetiloxi]-1λ^5-azabiciclo[2.2.2]octan-1-ilio
antagonista de los receptores muscarínicos

$C_{26}H_{30}BrNO_4S_2$ 320345-99-1



afimoxifenum
afimoxifene

4-(1-{4-[2-(dimethylamino)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol
antiestrogen

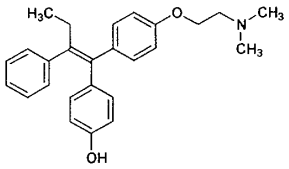
afimoxifène

4-[1-[4-[2-(diméthylamino)éthoxy]phényl]-2-phénylbut-1-ényl]phénol
antioestrogène

afimoxifeno

4-[1-[4-[2-(dimetilamino)etoxi]fenil]-2-fenilbut-1-enil]fenol
antiestrógeno

$C_{26}H_{29}NO_2$ 68392-35-8



and *Z* isomer
et l'isomère *Z*
y el isómero *Z*

afliberceptum*
aflibercept

des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 *C*-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
angiogenesis inhibitor

aflibercept

(211-211':214-214')-bisdisulfure du dimère de la dès-432-lysine-[récepteur 1 humain du facteur de croissance endothélial vasculaire-(103-204)-peptide (contenant le domaine Ig-like C2-type 2) protéine de fusion avec le récepteur 2 humain du facteur de croissance endothélial vasculaire-(206-308)-peptide (contenant un fragment du domaine Ig-like C2-type 3) protéine de fusion avec l'immunoglobuline G1 humaine-(227 résidus *C*-terminaux)-peptide (fragment Fc)]
inhibiteur de l'angiogénèse

aflibercept

(211-211':214-214')-bisdisulfuro del dímero de la des-432-lisina-[receptor 1 humano del factor de crecimiento endotelial vascular-(103-204)-péptido (que contiene el dominio Ig-like C2-tipo 2) proteína de fusión con el receptor 2 humano del factor de crecimiento endotelial vascular-(206-308)-péptido (que contiene un fragmento del dominio Ig-like C2-tipo 3) proteína de fusión con la inmunoglobulina G1 humana-(227 restos *C*-terminales)-péptido (fragmento Fc)]
inhibidor de la angiogenesis

$C_{4316}H_{6788}N_{1164}O_{1304}S_{32}$ 845771-78-0

Monomer / Monomère / Monómero

```
SDTGRPFVEM YSEIPEIIHM TEGRELVIPC RVTSPNITVT LKKFPLDTLI (50)
PDGKRIIWDS RKGFIISNAT YKEIGLLTCE ATVNGHLYKT NYLTHRQTNT (100)
IIDVVLSPSH GIELSVGEKL VLNCTARTEL NVGIDFNWEY PSSKHQHKKL (150)
VNRDLKTQSG SEMKKFLSTL TIDGVTRSDQ GLYTCAASSG LMTKKNSTFV (200)
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Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

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30-79 , 30-79 , 124-185 , 124-185 , 211-211 ,
214-214 , 246-306 , 246-306 , 352-410 , 352-410
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aleglitazarum
aleglitazar

(2*S*)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-benzothiophen-7-yl}propanoic acid
antidiabetic

aléglitazar

acide (2*S*)-2-méthoxy-3-[4-[2-(5-méthyl-2-phényl-1,3-oxazol-4-yl)=éthoxy]-1-benzothiophén-7-yl]propanoïque
antidiabétique

aleglitazar

ácido (2*S*)-3-{4-[2-(2-fenil-1,3-oxazol-5-metil-4-il)etoxi]-1-benzotiofen-7-il}-2-metoxipropanoico
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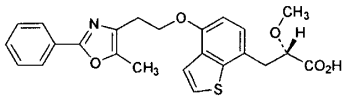
$C_{24}H_{23}NO_5S$ 475479-34-6



alferminogenum tadenovecum*
alferminogene tadenovec

Recombinant human adenovirus 5 (replication-deficient, E1-deleted) containing a human fibroblast growth factor-4 cDNA sequence driven by a cytomegalovirus promoter
gene therapy product - stimulates angiogenesis

alferminogène tadénovec

adénovirus 5 humain recombinant (réplication-déficient, région E1-supprimée) contenant la séquence ADN-copie du facteur 4 de croissance du fibroblaste humain sous contrôle d'un promoteur de cytomégalovirus
produit de thérapie génique stimulateur de l'angiogénèse

alferminogén tadenovec

adenovirus 5 humano recombinante (replicación-deficiente, con delección E1) que contiene la secuencia DNA-copia del factor-4 de crecimiento de fibroblastos humanos controlado por un promotor de citomegalovirus
producto para genoterapia,estimulante de la angiogénesis

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Expert Opinion

VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

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Background: Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD. In addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2. *Objective*: To review the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD. *Methods*: Literature review. *Results/conclusion*: VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. Two Phase III clinical trials (VIEW-1 and VIEW-2) comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide vital insight into the clinical applicability of this drug.

Keywords: aflibercept, AMD, angiogenesis, neovascularization, VEGF, VEGF inhibition, VEGF Trap

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1. Introduction

Age-related macular degeneration (AMD) affects > 1.75 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million [1]. Worldwide, AMD is estimated to affect 14 million people [2]. While the vast majority of patients suffering from AMD have the dry form, ~ 80 – 90% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease [3]. Until recently, healthcare professionals had few options when it came to treating neovascular AMD. For many years, subfoveal choroidal neovascularization (CNV) was treated with argon laser therapy according to guidelines from the Macular Photocoagulation Study [4-12]. This treatment, in the setting of subfoveal disease, was unsatisfactory for a number of reasons, including the limited benefits in visual stabilization and the high risk of inducing central vision deficits [13]. Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photosensitizing dye (verteporfin) to selectively target CNV. While more efficacious than previous treatments, patients receiving PDT failed to recover vision and continued to experience a decline in visual acuity [14] and the treatment was of questionable cost effectiveness [15].

The more recent development of agents that inhibit VEGF has largely supplanted these previous treatments. The pathogenesis of CNV in the setting of

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AMD is complex; however, there is overwhelming evidence that VEGF is a predominant mediator in its genesis. VEGF receptors are expressed by a number of important cell types in the eye, including vascular endothelial cells, choroidal fibroblasts, retinal pigment epithelial cells and inflammatory cells attracted by hypoxia [16-19]. Higher levels of VEGF expression have been demonstrated in animal models [20,21] and human studies of eyes with AMD [17,22-24] and antagonism of VEGF in both settings have definitively demonstrated inhibition of neovascularization and vascular permeability. VEGF-A is the predominant member of the VEGF family targeted by drugs currently in widespread use; however, the group is also comprised of VEGF-B, VEGF-C, VEFG-D and placental growth factors-1 and -2.

Systemic administration of bevacizumab is effective against neovascular AMD; however, systemic complications limit its use [25]. Accordingly, all anti-VEGF agents for neovascular AMD are administered only by intravitreal injection. The two largest studies examining anti-VEGF therapy, the MARINA [26] and the ANCHOR [27,28] trials, were randomized, controlled, double-masked Phase III clinical trials that together evaluated monthly ranibizumab for the treatment of all types of neovascular AMD. In both trials, 94% of patients with neovascular AMD lost fewer than 15 letters of visual acuity at 12 and 24 months when treated with ranibizumab. Surprisingly, as many as 40% of patients in the two trials improved by > 15 letters from baseline at 2 years. Ranibizumab received the FDA approval for all types of neovascular AMD in 2006. Based on the results of these two landmark studies, anti-VEGF therapies for neovascular AMD have largely replaced previous treatment modalities.

2. Background

2.1 Overview of the market (unmet needs, competitor compounds/in clinical development)

By far the most commonly used anti-VEGF drugs currently in use for neovascular AMD are ranibizumab and bevacizumab. Pegaptanib was the first anti-VEGF drug approved by the FDA for the treatment of AMD; however, it proved less efficacious than current treatments [13] (possibly due to its selective binding of VEGF-165) and is no longer widely used in most countries. Ranibizumab is the only drug in widespread use currently approved by the FDA for treatment of neovascular AMD and is by far the most extensively studied [26,27,29,30]. It is a recombinant monoclonal antibody fragment with a high binding affinity for all isotypes of VEGF-A. Bevacizumab, currently being used off-label for the treatment of AMD in the US, is a humanized whole antibody to VEGF-A used in oncology regimens that also binds all isotypes of VEGF-A. Although ranibizumab has been shown to have a higher affinity for VEGF-A, it is not clear if ranibizumab has superior efficacy to bevacizumab. Retrospective and small randomized studies have suggested similar efficacy profiles [31,32]. The Comparisons of Age-Related Macular Degeneration Treatment Trial (CATT) is a 2-year, multi-centered, randomized clinical trial comparing ranibizumab and bevacizumab for neovascular AMD. Enrollment began in February 2008. Despite the off-label status of bevacizumab, it continues to be a popular treatment choice in the US because of the significantly reduced price of treatment ($ 50 – 100 for bevacizumab versus $ 2000 for ranibizumab (2008 pricing)).

As previously mentioned, the MARINA [26] and the ANCHOR [27,28] trials examined the efficacy of ranibizumab when administered monthly. The time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules. In the PIER study [30], patients initially received monthly injections of ranibizumab for 3 months followed by quarterly injections. Although patient visual acuities actually improved at 3 months, during the quarterly dosing segment visual acuity returned to baseline. The PrONTO study [29] looked at as needed (p.r.n.) dosing of ranibizumab after three consecutive monthly doses. The need for further injections was made on the basis of recurrent CNV as evidenced by worsening vision, retinal thickening on ocular coherence tomography (OCT) or abnormalities on fluorescein angiogram (FA). At 2 years of follow up, 78% of patients had maintained vision and vision had improved by > 3 lines in 43% of patients with an average of five injections a year. These later studies seem to indicate that quarterly dosing is associated with poorer outcomes but it may be possible to extend the time between injections if the patient is frequently monitored. However, even with the p.r.n. dosing utilized in the PrONTO study, patients are still required to make monthly visits to the office with frequent and expensive testing.

The development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action. Most new compounds in development are targeted toward inhibition of various steps in the VEGF signaling pathway. There are a number of drugs in development that inhibit the downstream tyrosine kinase cascade activated by the binding of VEGF with its receptor (VEGFR). Vatalanib is an oral formulation that binds to all three VEGFRs and has recently completed Phase I/II study as adjuvant to PDT and ranibizumab [33]. Topical tyrosine kinase inhibitors currently undergoing Phase II clinical studies include pazopanib [34] and TG100801 [35]. Another approach utilizes siRNA to silence genes which express proteins involved in angiogenesis. Bevasiranib, an siRNA that targets VEGF-A mRNA, showed encouraging Phase I and II data, but the Phase III trial was halted in March 2009 for projected failure to meet the primary end point [36]. An extra antiangiogenic target being developed is pigment epithelium-derived factor (PEDF), a potent inhibitor of new vessel growth. AdGVPEDF.11D uses an adenovector to deliver the PEDF gene to target cells, resulting in the local production of PEDF in the treated eye. AdGVPEDF.11D has recently completed Phase I clinical trials [37]. Another

recently discovered alternative pathway for decreasing angiogenesis involves inhibition of nicotinic acetylcholine receptors. ATG3 (mecamylamine), a topical formulation that inhibits the nicotinic acetylcholine receptors, has shown promising results in animal and Phase I trials and is currently undergoing a Phase II study [25].

2.2 Introduction to compound

VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA) in the US and in collaboration with Bayer HealthCare (Leverkusen, Germany) in global markets. Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Figure 1). Functionally, VEGF Trap-Eye acts as a receptor decoy with high affinity for all VEGF isoforms, binding more tightly than their native receptors. Unlike anti-VEGF drugs currently in use, VEGF Trap-Eye is designed to inhibit placental growth factors-1 and -2 in addition to all isoforms of VEGF-A.

2.3 Chemistry

VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations. Both aflibercept and VEGF Trap-Eye are manufactured in bioreactors from industry standard Chinese hamster ovary cells that overexpress the fusion protein. However, VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye. VEGF Trap-Eye is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.

2.4 Pharmacodynamics

The aflibercept dose that is administered in oncology settings is either 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks, which corresponds to 2 mg/(kg week) with either schedule. The highest intravitreal dose being used in pivotal trials for VEGF Trap-Eye is 2 mg/month, which corresponds to at least a 280-fold lower potential systemic exposure than in the oncology setting. Early trials with aflibercept administered intravenously for AMD indicated that doses of 0.3 mg/kg (21 mg total) were inadequate to fully capture systemic VEGF. Thus, the low intravitreal dose of 2 mg allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated.

2.5 Pharmacokinetics and metabolism

Aflibercept is cleared from circulation through two pathways: by binding to VEGF to form an inactive VEGF–aflibercept complex and by Fc-receptor or pinocytotic mediated pathways that end in proteolysis, which are presumed to be similar to pathways that metabolize antibodies. At very high doses, free aflibercept has a terminal half-life of ~ 17 days in the circulation. The half-life of human intravitreal doses is unknown. Intravitreal primate doses of ranibizumab have a half-life of ~ 3 days [38]. At low blood levels, clearance of free aflibercept is rapid as a result of binding to VEGF with picomolar affinity [39].

2.6 Clinical efficacy

2.6.1 *Phase I*

A Phase I, randomized, double-blind, placebo-controlled trial of intravenous aflibercept (oncology formulation) was completed in 25 patients with AMD. Although systemic aflibercept did demonstrate a dose-dependent decrease in retinal thickness, the study was halted due to concerns of dose-dependent toxicity when one patient developed hypertension and another proteinuria [40].

The safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two-part Clinical Evaluation of Anti-angiogenesis in the Retina-1 (CLEAR-IT-1) study [41]. The first part was a sequential cohort dose-escalation study in which 21 patients were monitored for safety, changes in foveal thickness on OCT, best corrected visual acuity (BCVA) and lesion size on FA for 6 weeks. No adverse systemic or ocular events were noted and visual acuity remained stable or improved ≥ 3 lines in 95% of patients with a mean increase in BCVA of 4.6 letters at 6 weeks [42]. Patients showed substantially decreased foveal thickness [41].

In the second part, 30 patients received a single intravitreal injection of either 0.5 or 4 mg of VEGF Trap-Eye and were followed for 8 weeks. All patients were evaluated for their rates of retreatment, changes in BCVA, foveal thickness as well as change in total lesion size and area of CNV. Patients had ETDRS (Early Treatment of Diabetic Retinopathy Study) BCVA ranging from 20/40 to 20/320 with any angiographic subtype of CNV at baseline. No serious adverse events or ocular inflammation was identified during the study. At 8 weeks, the mean decrease in retinal thickness in the low dose group was 63.7 µm compared to 175 µm for the high dose group. Of the first 24 patients to complete the study, 11 out of 12 patients in the 0.5 mg dose group required retreatment in a median of 64 days, compared with 4 out of 12 in the 4 mg dose group who required retreatment in a median of 69 days [43].

VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of diabetic macular edema (DME) [44]. The drug was administered as a single 4 mg intravitreal injection to five patients with longstanding diabetes and several previous treatments for DME. The single injection resulted in a median decrease of central macular thickness measured by OCT of 79 µm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks.

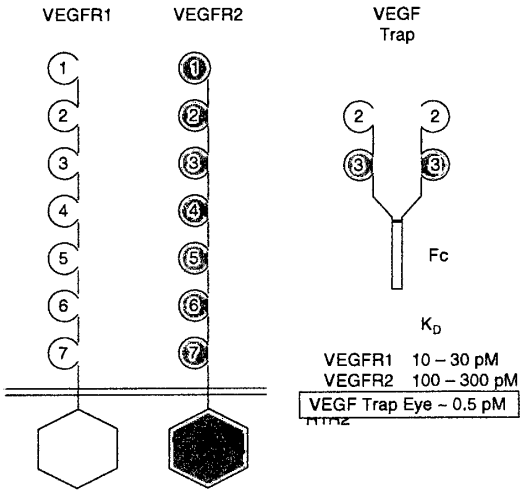

Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

2.6.2 *Phase II*

CLEAR-IT-2 trial [45] was a prospective, randomized, multi-center, controlled dose- and interval-ranging Phase II trial in which 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. The mean age of the group was 78.2 years and all angiographic subtypes of CNV were represented at baseline. The mean ETDRS BCVA in letters at baseline was 56. Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) and three groups received quarterly doses of either 0.5, 2.0 or 4.0 mg for 12 weeks (at weeks 0 and 12). Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness of ≥ 100 µm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks. During the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections. The median time to first reinjection in all groups was 110 days and 19% of patients required no more injections at week 52. Patients in these two monthly dosing groups also displayed mean decreases in retinal thickness versus baseline of 143 µm ($p < 0.0001$) in the 2.0 mg group and 125 µm ($p < 0.0001$) in the 0.5 mg group at 52 weeks as measured by OCT [45].

Patients in the three quarterly dosing groups also showed mean improvements in BCVA and retinal thickness; however, they were generally not as profound as the monthly injection group [45].

2.6.3 *Phase III*

A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

2.7 Safety and tolerability

Based on Phase II study data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events. In the 157 patients enrolled in CLEAR-IT 2 trial, there was one reported case of culture-negative endophthalmitis not deemed to be related to the study drug. There were also two deaths (one from pre-existing pulmonary hypertension and one from pancreatic carcinoma) and one arterial thromboembolic event (in a patient with a history of previous stroke) that occurred during the study period, but no serious systemic adverse events were deemed related to VEGF Trap-Eye administration. The most common adverse events reported in the study included conjunctival hemorrhage (38.2%), transient increased intraocular pressure (18.5%), refraction disorder (15.9%), retinal hemorrhage (14.6%), subjective visual acuity loss (13.4%), vitreous detachment (11.5%) and eye pain (9.6%) [45].

3. Conclusion

Anti-VEGF therapy has vastly improved the treatment of neovascular AMD in terms of both safety and efficacy. The ANCHOR [26] and MARINA [27,28] trials have established ranibizumab as an effective therapy when dosed monthly. It has been shown to stabilize vision in 94% of patients and in almost 40% of patients vision will actually improve by 3 or more lines. However, the monthly dosing schedules used in these trials present a financial and time burden to patients and healthcare practitioners. The more recent PIER [30] and

PrONTO [29] trials have shown that ranibizumab is less effective when dosed quarterly, but it may be possible to extend the time between injections when patients are followed closely with frequent examinations and ancillary testing. The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established but new treatments are aimed at extending and improving on the efficacy of ranibizumab. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-1 and -2. Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD. In Phase II study data, patients dosed in a similar fashion to the PrONTO trial demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year. Of the greatest interest, patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase. While this number is difficult to compare directly to the number of injections required during the p.r.n. phase of the PrONTO ranibizumab study, it is promising. A direct comparison of the efficacy of VEGF Trap-Eye versus ranibizumab will be possible with the completion of two Phase III trials, the VIEW-1 and -2 studies.

4. Expert opinion

The advent of anti-VEGF therapy for treatment of neovascular AMD has revolutionized therapy for a common blinding disease. Before the development of pegaptanib, ranibizumab and bevacizumab, the diagnosis of neovascular AMD portended a prognosis of nearly universal decline in vision, and frequently loss of useful vision in the affected eye.

Current treatment regimens with either ranibizumab or bevacizumab now afford stabilization of vision in > 90% of patients, with significant vision gain in one-third of all patients treated. There have been no significant, proven adverse systemic effects with the intraocular use of either drug. However, limitations of current therapy include the need for frequent intraocular injections, as often as monthly, without a defined stopping point. Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients during their treatment course.

Desirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals. For other indications, time-release delivery methods have met with some success, including the following agents: intraocular steroids, including polymeric fluocinolone and dexamethasone, lasting 3 years and 6 months, respectively [48-50], and for a single biologically active cytokine, ciliary neurotrophic factor, which is released for a period greater than 1 year by encapsulated, bioengineered, implanted cells [51]. While efforts are underway to develop encapsulated cell technology for sustained-release anti-VEGF therapy, no investigational drugs or devices have progressed yet to clinical trial enrollment.

VEGF Trap-Eye represents the most promising anti-VEGF investigational drug that is currently in Phase III trial. VEGF Trap-Eye, a decoy VEGF receptor protein, binds all isoforms of free VEGF with high affinity, in addition to placental growth factor. In contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF–VEGF Trap complex is relatively inert, and is degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.

Data from the Phase II study with VEGF Trap-Eye were positive and the results from the non-inferiority Phase III trials will establish its efficacy versus ranibizumab. Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals. If effective at 4 week intervals only, VEGF Trap-Eye will be adopted into clinical practice if it offers a competitive price advantage over ranibizumab. If effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, and would probably find wide acceptance. The second p.r.n. dosing stage of the Phase III trial will also provide insight into whether VEGF Trap-Eye offers longer duration of treatment effectiveness than ranibizumab.

Data from the VIEW-1 and VIEW-2 trials will need to be interpreted by clinicians in the context of emerging adjuvant therapies that may extend the time between anti-VEGF therapy injections. Many clinicians now treat patients with anti-VEGF therapies in combination with verteporfin PDT. Randomized, open-label studies and one large retrospective case series database seem to indicate lower retreatment rates and improved visual outcomes when compared with monotherapy [52-55]. As a result, at least two prospective, randomized trials are currently underway to further examine combination verteporfin PDT and anti-VEGF treatments [56,57]. An extra combination treatment currently under study is the use of epiretinal brachytherapy with Strontium-90 combined with bevacizumab. A recently published small pilot study showed good safety and efficacy with a single application of epiretinal radiation and two bevacizumab injections after 12 months [58]. A larger, multi-center Phase III trial is underway [59].

Anti-VEGF agents are currently only approved for the treatment of exudative AMD. The multifactorial nature of DME, including non-VEGF mediated causes such as pericyte and endothelial cell damage and tractional mechanisms, has made treatment of this condition difficult using current modalities. Clinical studies are underway with anti-VEGF agents in DME and retinal vein occlusion. VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion. The

FDA approval of VEGF Trap-Eye for these indications would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease.

Eventually, injectable agents targeting the VEGF pathway may be supplanted by implantable devices that deliver polymer-bound drug or manufacture the protein *in vivo*. Further therapies for neovascular AMD such as targeted radiation may confer extra treatment benefit. In the meantime, VEGF Trap-Eye is a promising investigational drug that, if approved, will improve ophthalmologists' ability to treat neovascular AMD.

Declaration of interest

SCN Oliver is a clinical investigator for Genentech and Alcon. JL Olson and N Mandava are clinical investigators for Genentech, Regeneron and Alcon.

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REGENERON PHARMACEUTICALS INC

FORM 10-Q
(Quarterly Report)

Filed 11/07/07 for the Period Ending 09/30/07

Address	777 OLD SAW MILL RIVER RD TARRYTOWN, NY 10591-6707
Telephone	9143477000
CIK	0000872589
Symbol	REGN
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-Q

(Mark One)

☑ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended September 30, 2007

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15 (d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission File Number 0-19034

REGENERON PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

New York	13-3444607
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
777 Old Saw Mill River Road Tarrytown, New York	10591-6707
(Address of principal executive offices)	(Zip Code)

(914) 347-7000

(Registrant's telephone number, including area code)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☑ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☑ Non-accelerated filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ☐ No ☑

Indicate the number of shares outstanding of each of the issuer's classes of common stock as of October 31, 2007:

Class of Common Stock	Number of Shares
Class A Stock, $0.001 par value	2,260,266
Common Stock, $0.001 par value	63,889,481

REGENERON PHARMACEUTICALS, INC.
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September 30, 2007

PART I. FINANCIAL INFORMATION
ITEM 1. FINANCIAL STATEMENTS

REGENERON PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS AT SEPTEMBER 30, 2007 AND DECEMBER 31, 2006 (Unaudited)
(In thousands, except share data)

	September 30, 2007	December 31, 2006
ASSETS		
Current assets		
Cash and cash equivalents	$ 97,416	$ 237,876
Marketable securities	299,566	221,400
Accounts receivable	10,968	7,493
Prepaid expenses and other current assets	14,070	3,215
Total current assets	422,020	469,984
Restricted cash	1,600	1,600
Marketable securities	98,710	61,983
Property, plant, and equipment, at cost, net of accumulated depreciation and amortization	49,358	49,353
Other assets	1,408	2,170
Total assets	$ 573,096	$ 585,090
LIABILITIES and STOCKHOLDERS' EQUITY		
Current liabilities		
Accounts payable and accrued expenses	$ 27,872	$ 21,471
Deferred revenue, current portion	68,814	23,543
Total current liabilities	96,686	45,014
Deferred revenue	125,013	123,452
Notes payable	200,000	200,000
Total liabilities	421,699	368,466
Commitments and contingencies		
Stockholders' equity		
Preferred stock, $.01 par value; 30,000,000 shares authorized; issued and outstanding-none		
Class A Stock, convertible, $.001 par value; 40,000,000 shares authorized; shares issued and outstanding - 2,260,266 in 2007 and 2,270,353 in 2006	2	2
Common Stock, $.001 par value; 160,000,000 shares authorized; shares issued and outstanding - 63,825,329 in 2007 and 63,130,962 in 2006	64	63
Additional paid-in capital	931,482	904,407
Accumulated deficit	(780,146)	(687,617)
Accumulated other comprehensive loss	(5)	(231)
Total stockholders' equity	151,397	216,624
Total liabilities and stockholders' equity	$ 573,096	$ 585,090

The accompanying notes are an integral part of the financial statements.

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

	Three months ended September 30,		Nine months ended September 30,	
	2007	2006	2007	2006
Revenues				
Contract research and development	$ 12,311	$ 11,448	$ 41,873	$ 41,026
Contract manufacturing		4,176		12,075
Technology licensing	10,000		18,421	
	22,311	15,624	60,294	53,101
Expenses				
Research and development	51,689	34,808	136,788	101,290
Contract manufacturing		3,054		7,716
General and administrative	9,289	6,019	26,426	18,264
	60,978	43,881	163,214	127,270
Loss from operations	(38,667)	(28,257)	(102,920)	(74,169)
Other income (expense)				
Investment income	5,840	3,858	19,424	11,023
Interest expense	(3,011)	(3,011)	(9,033)	(9,033)
	2,829	847	10,391	1,990
Net loss before cumulative effect of a change in accounting principle	(35,838)	(27,410)	(92,529)	(72,179)
Cumulative effect of adopting Statement of Financial Accounting Standards No. 123R ("SFAS 123R")				813
Net loss	$ (35,838)	$ (27,410)	$ (92,529)	$ (71,366)
Net loss per share amounts, basic and diluted:				
Net loss before cumulative effect of a change in accounting principle	$ (0.54)	$ (0.48)	$ (1.40)	$ (1.27)
Cumulative effect of adopting SFAS 123R				0.02
Net loss	$ (0.54)	$ (0.48)	$ (1.40)	$ (1.25)
Weighted average shares outstanding, basic and diluted	66,069	57,011	65,861	56,884

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENT OF STOCKHOLDERS' EQUITY (Unaudited)
For the nine months ended September 30, 2007
(In thousands)

	Class A Stock		Common Stock		Additional Paid-in	Accumulated	Accumulated Other Comprehensive	Total Stockholders'	Comprehensive
	Shares	Amount	Shares	Amount	Capital	Deficit	Loss	Equity	Loss
Balance, December 31, 2006	2,270	$ 2	63,131	$ 63	$ 904,407	$ (687,617)	$ (231)	$ 216,624	
Issuance of Common Stock in connection with exercise of stock options, net of shares tendered			619	1	5,170			5,171	
Issuance of Common Stock in connection with Company 401(k) Savings Plan contribution			65		1,367			1,367	
Conversion of Class A Stock to Common Stock	(10)		10						
Stock-based compensation expense					20,538			20,538	
Net loss						(92,529)		(92,529)	$ (92,529)
Change in net unrealized loss on marketable securities							226	226	226
Balance, September 30, 2007	2,260	$ 2	63,825	$ 64	$ 931,482	$ (780,146)	$ (5)	$ 151,397	$ (92,303)

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF CASH FLOWS (Unaudited)
(In thousands)

	Nine months ended September 30, 2007	2006
Cash flows from operating activities		
Net loss	$ (92,529)	$ (71,366)
Adjustments to reconcile net loss to net cash used in operating activities		
Depreciation and amortization	8,588	11,196
Non-cash compensation expense	20,538	13,542
Impairment charge on marketable securities	803	
Cumulative effect of a change in accounting principle		(813)
Changes in assets and liabilities		
(Increase) decrease in accounts receivable	(3,475)	28,581
(Increase) decrease in prepaid expenses and other assets	(11,876)	364
Decrease in inventory		3,524
Increase (decrease) in deferred revenue	46,832	(12,503)
Increase (decrease) in accounts payable, accrued expenses, and other liabilities	7,674	(2,753)
Total adjustments	69,084	41,138
Net cash used in operating activities	(23,445)	(30,228)
Cash flows from investing activities		
Purchases of marketable securities	(478,209)	(252,037)
Sales or maturities of marketable securities	363,739	261,749
Capital expenditures	(7,716)	(1,603)
Net cash (used in) provided by investing activities	(122,186)	8,109
Cash flows from financing activities		
Net proceeds from the issuance of Common Stock	5,171	4,883
Other		390
Net cash provided by financing activities	5,171	5,273
Net decrease in cash and cash equivalents	(140,460)	(16,846)
Cash and cash equivalents at beginning of period	237,876	184,508
Cash and cash equivalents at end of period	$ 97,416	$ 167,662

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

1. Interim Financial Statements

The interim Condensed Financial Statements of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company") have been prepared in accordance with the instructions to Form 10-Q and Article 10 of Regulation S-X. Accordingly, they do not include all information and disclosures necessary for a presentation of the Company's financial position, results of operations, and cash flows in conformity with accounting principles generally accepted in the United States of America. In the opinion of management, these financial statements reflect all adjustments, consisting only of normal recurring accruals, necessary for a fair presentation of the Company's financial position, results of operations, and cash flows for such periods. The results of operations for any interim periods are not necessarily indicative of the results for the full year. The December 31, 2006 Condensed Balance Sheet data were derived from audited financial statements, but do not include all disclosures required by accounting principles generally accepted in the United States of America. These financial statements should be read in conjunction with the financial statements and notes thereto contained in the Company's Annual Report on Form 10-K for the year ended December 31, 2006.

2. Per Share Data

The Company's basic and diluted net loss per share amounts have been computed by dividing net loss by the weighted average number of shares of Common Stock and Class A Stock outstanding. Net loss per share is presented on a combined basis, inclusive of Common Stock and Class A Stock outstanding, as each class of stock has equivalent economic rights. For the three and nine months ended September 30, 2007 and 2006, the Company reported net losses; therefore, no common stock equivalents were included in the computation of diluted net loss per share for these periods, since such inclusion would have been antidilutive. The calculations of basic and diluted net loss per share are as follows:

	Three Months Ended September 30,	
	2007	2006
Net loss (Numerator)	$(35,838)	$(27,410)
Weighted-average shares, in thousands (Denominator)	66,069	57,011
Basic and diluted net loss per share	$ (0.54)	$ (0.48)

	Nine Months Ended September 30,	
	2007	2006
Net loss (Numerator)	$(92,529)	$(71,366)
Weighted-average shares, in thousands (Denominator)	65,861	56,884
Basic and diluted net loss per share	$ (1.40)	$ (1.25)

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

Shares issuable upon the exercise of stock options, vesting of restricted stock awards, and conversion of convertible debt, which have been excluded from the September 30, 2007 and 2006 diluted per share amounts because their effect would have been antidilutive, include the following:

	Three months ended September 30,	
	2007	2006
Stock Options:		
Weighted average number, in thousands	15,153	14,082
Weighted average exercise price	$ 16.01	$ 14.35
Convertible Debt:		
Weighted average number, in thousands	6,611	6,611
Conversion price	$ 30.25	$ 30.25

	Nine months ended September 30,	
	2007	2006
Stock Options:		
Weighted average number, in thousands	15,308	14,220
Weighted average exercise price	$ 15.86	$ 14.31
Restricted Stock:		
Weighted average number, in thousands	—	31
Convertible Debt:		
Weighted average number, in thousands	6,611	6,611
Conversion price	$ 30.25	$ 30.25

3. Statement of Cash Flows

Supplemental disclosure of noncash investing and financing activities:

Included in accounts payable and accrued expenses at September 30, 2007 and December 31, 2006 are $0.9 million and $0.8 million, respectively, of accrued capital expenditures. Included in accounts payable and accrued expenses at September 30, 2006 and December 31, 2005 are $0.4 million and $0.2 million, respectively, of accrued capital expenditures.

Included in accounts payable and accrued expenses at December 31, 2006 and 2005 are $1.4 million and $1.9 million, respectively, of accrued Company 401(k) Savings Plan contribution expense. In the first quarter of 2007 and 2006, the Company contributed 64,532 and 120,960 shares, respectively, of Common Stock to the 401(k) Savings Plan in satisfaction of these obligations.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

Included in marketable securities at September 30, 2007 and December 31, 2006 are $2.5 million and $1.5 million, respectively, of accrued interest income. Included in marketable securities at September 30, 2006 and December 31, 2005 are $0.4 million and $1.2 million, respectively, of accrued interest income.

4. Accounts Receivable

Accounts receivable as of September 30, 2007 and December 31, 2006 consist of the following:

	September 30, 2007	December 31, 2006
Receivable from the sanofi-aventis Group	$ 7,075	$ 6,900
Receivable from National Institutes of Health	2,227	549
Receivable from Bayer HealthCare LLC	1,387	
Other	279	44
	$ 10,968	$ 7,493

5. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses as of September 30, 2007 and December 31, 2006 consist of the following:

	September 30, 2007	December 31, 2006
Accounts payable	$ 5,330	$ 4,349
Accrued payroll and related costs	7,837	9,932
Accrued clinical trial expense	5,084	2,606
Accrued expenses, other	4,579	2,292
Interest payable on convertible notes	5,042	2,292
	$ 27,872	$ 21,471

6. Comprehensive Loss

Comprehensive loss represents the change in net assets of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss of the Company includes net loss adjusted for the change in net unrealized gain (loss) on marketable securities. The net effect of income taxes on comprehensive loss is immaterial. For the three and nine months ended September 30, 2007 and 2006, the components of comprehensive loss are:

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

	Three months ended September 30,	
	2007	2006
Net loss	$(35,838)	$(27,410)
Change in net unrealized gain (loss) on marketable securities	511	378
Total comprehensive loss	$(35,327)	$(27,032)

	Nine months ended September 30,	
	2007	2006
Net loss	$(92,529)	$(71,366)
Change in net unrealized gain (loss) on marketable securities	226	375
Total comprehensive loss	$(92,303)	$(70,991)

7. Accounting for Collaboration with Bayer HealthCare

In October 2006, the Company entered into a license and collaboration agreement with Bayer HealthCare LLC to globally develop and commercialize outside the United States the Company's VEGF Trap for the treatment of eye disease by local administration ("VEGF Trap-Eye"). Under the terms of the agreement, Bayer made a non-refundable up-front payment to the Company of $75.0 million. In 2007, agreed upon VEGF Trap-Eye development expenses incurred by both companies under a global development plan will be shared as follows: Up to the first $50.0 million will be shared equally; Regeneron is solely responsible for the next $40.0 million; over $90.0 million will be shared equally. Through September 30, 2007, reimbursements from Bayer HealthCare of the Company's VEGF Trap-Eye development expenses totaled $12.9 million, of which $1.4 million was receivable at September 30, 2007. Neither party was reimbursed for any development expenses that it incurred prior to 2007. In addition, in August 2007, the Company received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in the neovascular form of age-related macular degeneration ("wet AMD").

The Company and Bayer HealthCare are currently formalizing the global development plans for the VEGF Trap-Eye in wet AMD and diabetic macular edema. The plans will include estimated development steps, timelines, and costs, as well as the projected responsibilities of and costs to be incurred by each of the companies. Pending completion of these plans, all payments received or receivable by the Company from Bayer HealthCare through September 30, 2007, totaling $107.9 million, have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, the Company will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in the Company's Statement of Operations. In the period when the Company commences recognizing previously deferred payments from Bayer HealthCare, the Company anticipates recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

8. 2007 License Agreements

AstraZeneca

In February 2007, the Company entered into a non-exclusive license agreement with AstraZeneca UK Limited that allows AstraZeneca to utilize the Company's *VelocImmune* ® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, AstraZeneca made a $20.0 million non-refundable up-front payment to the Company which was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. AstraZeneca also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. These additional payments will be recognized as revenue ratably over their respective annual license periods. The Company is entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by AstraZeneca using the Company's *VelocImmune* technology. For the nine months ended September 30, 2007, the Company recognized $12.1 million of revenue in connection with the AstraZeneca license agreement. At September 30, 2007, deferred revenue was $7.9 million.

Astellas

In March 2007, the Company entered into a non-exclusive license agreement with Astellas Pharma Inc. that allows Astellas to utilize the Company's *VelocImmune* technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, Astellas made a $20.0 million non-refundable up-front payment to the Company, which was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. Astellas also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. These additional payments will be recognized as revenue ratably over their respective annual license periods. The Company is entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by Astellas using the Company's *VelocImmune* technology. For the nine months ended September 30, 2007, the Company recognized $6.3 million of revenue in connection with the Astellas license agreement. At September 30, 2007, deferred revenue was $13.7 million.

9. Income Taxes

Effective January 1, 2007, the Company adopted the provisions of Financial Accounting Standards Board ("FASB") Interpretation No. 48 ("FIN 48"), *Accounting for Uncertainty in Income Taxes — an interpretation of FASB Statement No. 109.* The implementation of FIN 48 had

no impact on the Company's financial statements as the Company has no unrecognized tax benefits.

The Company is primarily subject to U.S. federal and New York State income tax. The Company's 1992 and subsequent tax years remain open to examination by U.S. federal and state tax authorities.

The Company's policy is to recognize interest and penalties related to income tax matters in income tax expense. As of January 1 and September 30, 2007, the Company had no accruals for interest or penalties related to income tax matters.

10. Legal Matters

From time to time, the Company is a party to legal proceedings in the course of the Company's business. The Company does not expect any such current legal proceedings to have a material adverse effect on the Company's business or financial condition.

11. Segment Information

Through 2006, the Company's operations were managed in two business segments: research and development, and contract manufacturing.

Research and development: Includes all activities related to the discovery of pharmaceutical products for the treatment of serious medical conditions, and the development and commercialization of these discoveries. Also includes revenues and expenses related to activities conducted under contract research and technology licensing agreements.

Contract manufacturing: Includes all revenues and expenses related to the commercial production of products under contract manufacturing arrangements. During 2006, the Company produced a vaccine intermediate for Merck & Co., Inc. under a manufacturing agreement, which expired in October 2006.

Due to the expiration of the Company's manufacturing agreement with Merck in October 2006, beginning in 2007, the Company only has a research and development business segment. Therefore, segment information has not been provided for 2007 in the table below.

The following table presents information about reported segments for the three and nine months ended September 30, 2006.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

	Three months ended September 30, 2006			
	Research & Development	Contract Manufacturing	Reconciling Items	Total
Revenues	$ 11,448	$ 4,176	—	$ 15,624
Depreciation and amortization	3,447	—(1)	$ 261	3,708
Non-cash compensation expense	4,632	130	—	4,762
Interest expense	—	—	3,011	3,011
Net (loss) income	(29,379)	1,122	847(2)	(27,410)
Capital expenditures	441	—	—	441

	Nine months ended September 30, 2006			
	Research & Development	Contract Manufacturing	Reconciling Items	Total
Revenues	$ 41,026	$12,075	—	$ 53,101
Depreciation and amortization	10,413	—(1)	$ 783	11,196
Non-cash compensation expense	13,220	322	(813) (3)	12,729
Interest expense	—	—	9,033	9,033
Net (loss) income	(78,528)	4,359	2,803(2)	(71,366)
Capital expenditures	1,409	—	—	1,409
Total assets	57,530	1,445	296,211(4)	355,186

(1) Depreciation and amortization related to contract manufacturing was capitalized into inventory and included in contract manufacturing expense when the product was shipped.

(2) Represents investment income, net of interest expense related primarily to convertible notes issued in October 2001. For the nine months ended September 30, 2006, also includes the cumulative effect of adopting Statement of Financial Accounting Standards No. ("SFAS") 123R, *Share-Based Payment.*

(3) Represents the cumulative effect of adopting SFAS 123R.

(4) Includes cash and cash equivalents, marketable securities, restricted cash (where applicable), prepaid expenses and other current assets, and other assets.

12. Future Impact of Recently Issued Accounting Standards

In February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities* . SFAS 159 permits entities to choose to measure many financial instruments and certain other items at fair value. The objective is to improve financial reporting by providing entities with the opportunity to mitigate volatility in reported earnings caused by measuring related assets and liabilities differently without having to apply complex hedge accounting provisions. SFAS 159 is effective for financial statements issued for fiscal years beginning after November 15, 2007. The Company will be required to adopt SFAS 159 effective

for the fiscal year beginning January 1, 2008. Management is currently evaluating the potential impact of adopting SFAS 159 on the Company's financial statements.

In June 2007, the Emerging Issues Task Force issued Statement No. 07-3, *Accounting for Non-refundable Advance Payments for Goods or Services to Be Used in Future Research and Development Activities* ("EITF 07-3"). EITF 07-3 addresses how entities involved in research and development activities should account for the non-refundable portion of an advance payment made for future research and development activities and requires that such payments be deferred and capitalized, and recognized as an expense when the goods are delivered or the related services are performed. EITF 07-3 is effective for fiscal years beginning after December 15, 2007, including interim periods within those fiscal years. The Company will be required to adopt EITF 07-3 effective for the fiscal year beginning January 1, 2008. Management believes that the future adoption of EITF 07-3 will not have a material impact on the Company's financial statements.

13. Subsequent Events

Purchase of Building – Rensselaer, New York

In June 2007, the Company exercised a purchase option on a building in Rensselaer, New York, in which the Company leased manufacturing, office, and warehouse space in a portion of the building. The Company completed the purchase of this property (land and building) in October 2007 at a cost of approximately $9 million.

Amendment to Operating Lease – Tarrytown, New York Facilities

The Company leases laboratory and office facilities in Tarrytown, New York. In December 2006, the Company entered into a new agreement to lease laboratory and office space that is now under construction and expected to be completed in mid-2009 at the Company's current Tarrytown location, plus retain a portion of the Company's existing space. In October 2007, the Company amended the December 2006 operating lease agreement to increase the amount of new space the Company will lease. The term of the lease is now expected to commence in mid-2008 and will expire approximately 16 years later. Other terms and conditions, as previously described in the Company's Form 10-K for the year ended December 31, 2006, remain unchanged.

In connection with these two subsequent events, the Company's previously disclosed total estimated future minimum noncancelable lease commitments under operating leases, as per the Company's Form 10-K for the year ended December 31, 2006, will decrease to $4.6 million and $9.3 million for the years ended December 31, 2008 and 2009, respectively, and increase to $14.2 million and $14.4 million for the years ended December 31, 2010 and 2011, respectively, and to $204.2 million, in the aggregate, for years subsequent to 2011.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The discussion below contains forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron Pharmaceuticals, Inc. and actual events or results may differ materially. These statements concern, among other things, the possible success and therapeutic applications of our product candidates and research programs, the timing and nature of the clinical and research programs now underway or planned, and the future sources and uses of capital and our financial needs. These statements are made by us based on management's current beliefs and judgment. In evaluating such statements, stockholders and potential investors should specifically consider the various factors identified under the caption "Risk Factors" which could cause actual results to differ materially from those indicated by such forward-looking statements. We do not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required by law.

Overview

Regeneron Pharmaceuticals, Inc. is a biopharmaceutical company that discovers, develops, and intends to commercialize pharmaceutical products for the treatment of serious medical conditions. We are currently focused on three development programs: rilonacept (IL-1 Trap) in various inflammatory indications, aflibercept (VEGF Trap) in oncology and the VEGF Trap-Eye formulation in eye diseases using intraocular delivery. Aflibercept is being developed in oncology in collaboration with the sanofi-aventis Group. The VEGF Trap-Eye is being developed in collaboration with Bayer HealthCare LLC. Our preclinical research programs are in the areas of oncology and angiogenesis, ophthalmology, metabolic and related diseases, muscle diseases and disorders, inflammation and immune diseases, bone and cartilage, pain, and cardiovascular diseases. We expect that our next generation of product candidates will be based on our proprietary technologies for developing human monoclonal antibodies. Developing and commercializing new medicines entails significant risk and expense. Since inception, we have not generated any sales or profits from the commercialization of any of our product candidates.

Our core business strategy is to maintain a strong foundation in basic scientific research and discovery-enabling technology and combine that foundation with our manufacturing and clinical development capabilities to build a successful, integrated biopharmaceutical company. We believe that our ability to develop product candidates is enhanced by the application of our technology platforms. Our discovery platforms are designed to identify specific genes of therapeutic interest for a particular disease or cell type and validate targets through high-throughput production of mammalian models. Our human monoclonal antibody technology (*VelocImmune* ®) and cell line expression technologies may then be utilized to design and produce new product candidates directed against the disease target. Based on the *VelocImmune* platform which we believe, in conjunction with our other proprietary technologies, can accelerate the development of fully human monoclonal antibodies, we plan to move our first new antibody product candidate into clinical trials in the fourth quarter of 2007. We plan to introduce two new antibody product candidates into clinical development each year, beginning in 2008. We continue to invest in the development of enabling technologies to assist in our efforts to identify, develop, and commercialize new product candidates.

Clinical Programs:

Below is a summary of the status of our clinical candidates:

1. Rilonacept – Inflammatory Diseases

Rilonacept (IL-1 Trap) is a protein-based product candidate designed to bind the interleukin-1 (called IL-1) cytokine and prevent its interaction with cell surface receptors. We are evaluating rilonacept in a number of diseases and disorders where IL-1 may play an important role, including a group of rare diseases called Cryopyrin-Associated Periodic Syndromes (CAPS) and other diseases associated with inflammation.

We recently submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for rilonacept in CAPS. In August 2007, the FDA granted priority review status to the BLA for rilonacept for the long-term treatment of CAPS. The FDA previously granted Orphan Drug status and Fast Track designation to rilonacept for the treatment of CAPS. In July 2007, rilonacept also received Orphan Drug designation in the European Union for the treatment of CAPS. In November 2007, we announced that we received notification from the FDA that the action date for the FDA's priority review of the BLA for rilonacept had been extended three months to February 29, 2008.

CAPS represents a group of rare inherited auto-inflammatory conditions, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). CAPS also includes Neonatal Onset Multisystem Inflammatory Disease (NOMID). Rilonacept has not been studied, and is not expected to be indicated, for the treatment of NOMID. The syndromes included in CAPS are characterized by spontaneous, systemic inflammation and are termed auto-inflammatory disorders. A novel feature of these conditions (particularly FCAS and MWS) is that exposure to mild degrees of cold temperature can provoke a major inflammatory episode that occurs within hours. CAPS is caused by a range of mutations in the gene *CIAS1* (also known as NLRP3) which encodes a protein named cryopyrin. Currently, there are no medicines approved for the treatment of CAPS.

We recently reported positive results from an exploratory proof of concept study of rilonacept in ten patients with chronic active gout. In those patients, treatment with rilonacept demonstrated a statistically significant reduction in patient pain scores in the single-blind, placebo-controlled study. Mean patients' pain scores, the key symptom measure in persistent gout, were reduced 41% ($p=0.025$) during the first two weeks of active treatment and reduced 56% ($p<0.004$) after six weeks of active treatment. In this study, in which safety was the primary endpoint measure, treatment with rilonacept was generally well-tolerated. We have initiated a Phase 2 safety and efficacy trial of rilonacept in the prevention of gout flares induced by the initiation of uric acid-lowering drug therapy used to control the disease.

We are also evaluating the potential use of rilonacept in other indications in which IL-1 may play a role, and are preparing to initiate exploratory proof-of-concept studies in anemia and other indications. The first of these studies will be in the treatment of anemia associated with chronic inflammation, which we plan to begin in the fourth quarter of 2007.

Under a March 2003 collaboration agreement with Novartis Pharma AG, we retain the right to elect to collaborate in the future development and commercialization of a Novartis IL-1 antibody, which is in clinical development. Following completion of Phase 2 development and submission to us of a written report on the Novartis IL-1 antibody, we have the right, in consideration for an opt-in payment, to elect to co-develop and co-commercialize the Novartis IL-1 antibody in North America. If we elect to exercise this right, we are responsible for paying 45% of post-election North American development costs for the antibody product. In return, we are entitled to co-promote the Novartis IL-1 antibody and to receive 45% of net profits on sales of the antibody product in North America. Under certain circumstances, we are also entitled to receive royalties on sales of the Novartis IL-1 antibody in Europe.

Under the collaboration agreement, Novartis has the right to elect to collaborate in the development and commercialization of a second generation rilonacept following completion of its Phase 2 development, should we decide to clinically develop such a second generation product candidate. Novartis does not have any rights or options with respect to our rilonacept currently in clinical development.

2. Aflibercept (VEGF Trap) – Oncology

Aflibercept is a protein-based product candidate designed to bind all forms of Vascular Endothelial Growth Factor-A (called VEGF-A, also known as Vascular Permeability Factor or VPF) and the related Placental Growth Factor (called PlGF), and prevent their interaction with cell surface receptors. VEGF-A (and to a less validated degree, PlGF) is required for the growth of new blood vessels that are needed for tumors to grow and is a potent regulator of vascular permeability and leakage.

Aflibercept is being developed in cancer indications in collaboration with sanofi-aventis. We and sanofi-aventis began the first two trials of our global Phase 3 development program in the third quarter of 2007. One trial will evaluate aflibercept in combination with docetaxel/prednisone in patients with 1 st line metastatic androgen independent prostate cancer. The other trial will evaluate aflibercept in combination with docetaxel in patients with 2 nd line metastatic non-small cell lung cancer. The companies plan to initiate two additional Phase 3 trials before the end of 2007 in first-line metastatic pancreatic cancer in combination with gemcitabine-based regimen and second-line metastatic colorectal cancer in combination with FOLFIRI (Folinic Acid (leucovorin), 5-fluorouracil, and irinotecan). In all of these trials, aflibercept is being combined with the current standard of chemotherapy care for the stated development stage of the cancer type.

The collaboration is conducting a number of other trials in the global development program for aflibercept. Five safety and tolerability studies of aflibercept in combination with standard chemotherapy regimens are continuing in a variety of cancer types to support the Phase 3 clinical program. Sanofi-aventis has also expanded the development program to Japan, where they are conducting a Phase 1 safety and tolerability study in combination with S-1 in patients with advanced solid malignancies.

The collaboration is also conducting Phase 2 single-agent studies in advanced ovarian cancer (AOC), non-small cell lung adenocarcinoma (NSCLA), and AOC patients with symptomatic malignant ascites (SMA). The AOC and NSCLA trials are fully enrolled and ongoing. The

SMA trial is approximately 50% enrolled and continues to enroll patients. In 2004, the FDA granted Fast Track designation to aflibercept for the treatment of SMA.

In addition, currently underway or scheduled to begin are more than 10 studies to be conducted in conjunction with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) evaluating aflibercept as a single agent or in combination with chemotherapy regimens in a variety of cancer indications.

The development program in oncology is expected to total over $400 million over the next several years. These expenses will be funded by sanofi-aventis in accordance with the terms of our collaboration agreement described below.

The first registration submission to a regulatory agency for aflibercept is possible as early as 2008, potentially as third line treatment as a single agent in advanced ovarian cancer (AOC). However, in order for our ongoing Phase 2 study in AOC to be sufficient to support such a submission, we believe that the final unblinded results of the study would have to demonstrate a more robust response rate than that reported in the interim analysis of blinded data from the study presented in June 2007 at the annual meeting of the American Society of Clinical Oncology (ASCO).

Cancer is a heterogeneous set of diseases and one of the leading causes of death in the developed world. A mutation in any one of dozens of normal genes can eventually result in a cell becoming cancerous; however, a common feature of cancer cells is that they need to obtain nutrients and remove waste products, just as normal cells do. The vascular system normally supplies nutrients to and removes waste from normal tissues. Cancer cells can use the vascular system either by taking over preexisting blood vessels or by promoting the growth of new blood vessels (a process known as angiogenesis). VEGF is secreted by many tumors to stimulate the growth of new blood vessels to supply nutrients and oxygen to the tumor. VEGF blockers have been shown to inhibit new vessel growth; and, in some cases, can cause regression of existing tumor vasculature. Countering the effects of VEGF, thereby blocking the blood supply to tumors, has demonstrated therapeutic benefits in clinical trials. This approach of inhibiting angiogenesis as a mechanism of action for an oncology medicine was validated in February 2004, when the FDA approved Genentech, Inc.'s VEGF inhibitor, Avastin ®. Avastin ® (a trademark of Genentech, Inc.) is an antibody product designed to inhibit VEGF and interfere with the blood supply to tumors.

Collaboration with the sanofi-aventis Group

In September 2003, we entered into a collaboration agreement with Aventis Pharmaceuticals, Inc. (predecessor to sanofi-aventis U.S.) to collaborate on the development and commercialization of aflibercept in all countries other than Japan, where we retained the exclusive right to develop and commercialize aflibercept. In January 2005, we and sanofi-aventis amended the collaboration agreement to exclude, from the scope of the collaboration, the development and commercialization of aflibercept for intraocular delivery to the eye. In December 2005, we and sanofi-aventis amended our collaboration agreement to expand the territory in which the companies are collaborating on the development of aflibercept to include Japan. Under the collaboration agreement, as amended, we and sanofi-aventis will share co-promotion rights and profits on sales, if any, of aflibercept outside of Japan for disease

indications included in our collaboration. In Japan, we are entitled to a royalty of approximately 35% on annual sales of aflibercept, subject to certain potential adjustments. We may also receive up to $400.0 million in milestone payments upon receipt of specified marketing approvals. This total includes up to $360.0 million in milestone payments related to receipt of marketing approvals for up to eight aflibercept oncology and other indications in the United States or the European Union. Another $40.0 million of milestone payments relate to receipt of marketing approvals for up to five oncology indications in Japan.

Under the collaboration agreement, as amended, agreed upon worldwide development expenses incurred by both companies during the term of the agreement will be funded by sanofi-aventis. If the collaboration becomes profitable, we will be obligated to reimburse sanofi-aventis for 50% of aflibercept development expenses in accordance with a formula based on the amount of development expenses and our share of the collaboration profits and Japan royalties, or at a faster rate at our option.

3. VEGF Trap – Eye Diseases

The VEGF Trap-Eye is a form of the VEGF Trap that has been purified and formulated with excipients and at concentrations suitable for direct injection into the eye. The VEGF Trap-Eye currently is being tested in a Phase 3 trial in patients with the neovascular form of age-related macular degeneration (wet AMD) and has completed a small pilot study in patients with diabetic macular edema (DME).

In the clinical development program for the VEGF Trap-Eye, we and Bayer HealthCare have initiated a Phase 3 study of the VEGF Trap-Eye in wet AMD. This first trial, known as VIEW 1 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), is comparing the VEGF Trap-Eye and Genentech, Inc.'s Lucentis ® (ranibizumab), an anti-angiogenic agent approved for use in wet AMD. This Phase 3 trial is evaluating dosing intervals of four and eight weeks for the VEGF Trap-Eye compared with ranibizumab dosed according to its label every four weeks. We and Bayer HealthCare plan to initiate a second Phase 3 trial in wet AMD in the first quarter of 2008. This second trial will be conducted primarily in the European Union and other parts of the world outside the U.S.

In October 2007, we and Bayer HealthCare announced positive results from the full analysis of the primary 12-week endpoint of a Phase 2 study evaluating the VEGF Trap-Eye in wet AMD. The VEGF Trap-Eye met the primary study endpoint of a statistically significant reduction in retinal thickness, a measure of disease activity, after 12 weeks of treatment compared with baseline (all five dose groups combined, mean decrease of 119 microns, $p<0.0001$). The mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.7 letters, $p<0.0001$). Preliminary analyses at 16 weeks showed that the VEGF Trap-Eye, dosed monthly, achieved a mean gain in visual acuity of 9.3 to 10 letters (for the 0.5 and 2 mg dose groups, respectively). In additional exploratory analyses, the VEGF Trap-Eye, dosed monthly, reduced the proportion of patients with vision of 20/200 or worse (a generally accepted definition for legal blindness) from 14.3% at baseline to 1.6% at week 16; the proportion of patients with vision of 20/40 or better (part of the legal minimum requirement for an unrestricted driver's license in the U.S.) was likewise increased from 19.0% at baseline to 49.2% at 16 weeks. These findings were presented at the Retina Society Conference.

We and Bayer HealthCare are also developing the VEGF Trap-Eye in DME and expect to initiate a Phase 3 study in DME in mid-2008. In May 2007, at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), the companies reported results from a small pilot study of the VEGF Trap-Eye in patients with DME. In the study, the VEGF Trap-Eye was well tolerated and demonstrated activity in five patients, with decreases in retinal thickness and improvement in visual acuity.

VEGF-A both stimulates angiogenesis and increases vascular permeability. It has been shown in preclinical studies to be a major pathogenic factor in both wet AMD and diabetic retinopathy, and it is believed to be involved in other medical problems affecting the eyes. In clinical trials, blocking VEGF-A has been shown to be effective in patients with wet AMD, and Macugen ® (OSI Pharmaceuticals, Inc.) and Lucentis ® (Genentech, Inc.) have been approved to treat patients with this condition.

Wet AMD and diabetic retinopathy (DR) are two of the leading causes of adult blindness in the developed world. In both conditions, severe visual loss is caused by a combination of retinal edema and neovascular proliferation. DR is a major complication of diabetes mellitus that can lead to significant vision impairment. DR is characterized, in part, by vascular leakage, which results in the collection of fluid in the retina. When the macula, the central area of the retina that is responsible for fine visual acuity, is involved, loss of visual acuity occurs. This is referred to as diabetic macular edema (DME). DME is the most prevalent cause of moderate visual loss in patients with diabetes.

Collaboration with Bayer HealthCare LLC

In October 2006, we entered into a collaboration agreement with Bayer HealthCare for the global development and commercialization outside the United States of the VEGF Trap-Eye. Under the agreement, we and Bayer HealthCare will collaborate on, and share the costs of, the development of the VEGF Trap-Eye through an integrated global plan that encompasses wet AMD, diabetic eye diseases, and other diseases and disorders. Bayer HealthCare will market the VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of the VEGF Trap-Eye. If the VEGF Trap-Eye is granted marketing authorization in a major market country outside the United States, we will be obligated to reimburse Bayer HealthCare for 50% of the development costs that it has incurred under the agreement from our share of the collaboration profits. Within the United States, we retained exclusive commercialization rights to the VEGF Trap-Eye and are entitled to all profits from any such sales. We received an up-front payment of $75.0 million from Bayer HealthCare. In August 2007, we received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in wet AMD, and can earn up to $90.0 million in additional development and regulatory milestones related to the development of the VEGF Trap-Eye and marketing approvals in major market countries outside the United States. We can also earn up to $135.0 million in sales milestones if total annual sales of the VEGF Trap-Eye outside the United States achieve certain specified levels starting at $200.0 million.

General

Developing and commercializing new medicines entails significant risk and expense. Since inception we have not generated any sales or profits from the commercialization of any of our product candidates and may never receive such revenues. Before revenues from the commercialization of our product candidates can be realized, we (or our collaborators) must overcome a number of hurdles which include successfully completing research and development and obtaining regulatory approval from the FDA and regulatory authorities in other countries. In addition, the biotechnology and pharmaceutical industries are rapidly evolving and highly competitive, and new developments may render our products and technologies uncompetitive or obsolete.

From inception on January 8, 1988 through September 30, 2007, we had a cumulative loss of $780.1 million. In the absence of revenues from the commercialization of our product candidates or other sources, the amount, timing, nature, and source of which cannot be predicted, our losses will continue as we conduct our research and development activities. We expect to incur substantial losses over the next several years as we continue the clinical development of the VEGF Trap-Eye and rilonacept; advance new product candidates into clinical development from our existing research programs utilizing our technology for designing fully human monoclonal antibodies; continue our research and development programs; and commercialize product candidates that receive regulatory approval, if any. Also, our activities may expand over time and require additional resources, and we expect our operating losses to be substantial over at least the next several years. Our losses may fluctuate from quarter to quarter and will depend on, among other factors, the progress of our research and development efforts, the timing of certain expenses, and the amount and timing of payments that we receive from collaborators.

The planning, execution, and results of our clinical programs are significant factors that can affect our operating and financial results. In our clinical programs, key events for 2007 and plans over the next 12 months are as follows:

Clinical Program	2007 Events to Date	2007-8 Plans
Rilonacept (IL-1 Trap)	• Completed the 24-week open-label safety extension phase of the Phase 3 trial in CAPS • FDA accepted BLA submission for CAPS • Granted Orphan Drug designation in CAPS in European Union • Reported positive results in exploratory proof-of-concept study in patients with chronic active gout • Initiated Phase 2 trial evaluating safety and efficacy of rilonacept in preventing gout-induced flares in patients initiating allopurinol therapy	• Receive FDA review decision to BLA submission for CAPS (expected in February 2008) • Initiate exploratory proof-of- concept study of rilonacept in a new indication • Evaluate rilonacept in other disease indications in which IL-1 may play an important role

Clinical Program	2007 Events to Date	2007-8 Plans
Aflibercept (VEGF Trap) — Oncology	• NCI/CTEP initiated more than 10 studies of the aflibercept as a single agent • Reported interim results from two Phase 2 single-agent trials – in advanced ovarian cancer and in non-small cell lung adenocarcinoma • Initiated Japanese Phase 1 trial of aflibercept in combination with S-1 in patients with solid malignancies • Sanofi-aventis initiated two Phase 3 trials of aflibercept in combination with standard chemotherapy regimens	• Sanofi-aventis to initiate two additional Phase 3 studies of aflibercept in combination with standard chemotherapy regimens in specific cancer indications • NCI/CTEP to initiate additional new exploratory safety and efficacy studies
VEGF Trap-Eye (intravitreal injection)	• Initiated first Phase 3 trial in wet AMD in patients in the U.S. and Canada • Reported positive primary endpoint results and preliminary extended treatment results of Phase 2 trial in wet AMD • Reported positive results in Phase 1 trial in DME	• Initiate second Phase 3 trial in wet AMD in the European Union and other countries around the world • Initiate Phase 3 trial in DME • Explore additional eye disease indications
VelocImmune ®		• Initiate first trial for antibody product candidate • Finalize plans to initiate clinical trials for two additional antibody candidates in 2008

License Agreements

AstraZeneca

In February 2007, we entered into a non-exclusive license agreement with AstraZeneca UK Limited that allows AstraZeneca to utilize our *VelocImmune* ® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, AstraZeneca made a $20.0 million non-refundable up-front payment to us. AstraZeneca also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. We are entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by AstraZeneca using our *VelocImmune* technology.

Astellas

In March 2007, we entered into a non-exclusive license agreement with Astellas Pharma Inc. that allows Astellas to utilize our *VelocImmune* technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, Astellas made a $20.0 million non-refundable up-front payment to us. Astellas also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. We are entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by Astellas using our *VelocImmune* technology.

Accounting for Collaboration with Bayer HealthCare

As described above, in October 2006 we entered into a VEGF Trap-Eye license and collaboration agreement with Bayer HealthCare. Under the terms of the agreement, Bayer HealthCare made a non-refundable up-front payment to us of $75.0 million. In August 2007, we received a $20.0 million development milestone payment from Bayer HealthCare, as described above. In 2007, agreed upon VEGF Trap-Eye development expenses incurred by both companies under a global development plan will be shared as follows: Up to the first $50.0 million will be shared equally; Regeneron is solely responsible for the next $40.0 million; over $90.0 million will be shared equally. Through September 30, 2007, reimbursements from Bayer HealthCare of our VEGF Trap-Eye development expenses total $12.9 million, of which $1.4 million was receivable at September 30, 2007. Neither party was reimbursed for any development expenses that it incurred prior to 2007.

We and Bayer HealthCare are currently formalizing our global development plans for the VEGF Trap-Eye in wet AMD and DME. The plans will include estimated development steps, timelines, and costs, as well as the projected responsibilities of and costs to be incurred by each of the companies. Pending completion of these plans, all payments received or receivable from Bayer HealthCare through September 30, 2007, totaling $107.9 million, have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, we will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments from Bayer (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in our Statement of Operations. In the period when we commence recognizing previously deferred payments from Bayer HealthCare, we anticipate recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

Results of Operations

Three Months Ended September 30, 2007 and 2006

Net Loss:

Regeneron reported a net loss of $35.8 million, or $0.54 per share (basic and diluted), for the third quarter of 2007 compared to a net loss of $27.4 million, or $0.48 per share (basic and diluted), for the third quarter of 2006.

Revenues:

Revenues for the three months ended September 30, 2007 and 2006 consist of the following:

(In millions)	2007	2006	Increase (Decrease)
Contract research & development revenue			
The sanofi-aventis Group	$ 9.2	$ 10.0	$ (0.8)
Other	3.1	1.4	1.7
Total contract research & development revenue	12.3	11.4	0.9
Contract manufacturing revenue		4.2	(4.2)
Technology licensing revenue	10.0		10.0
Total revenue	$ 22.3	$ 15.6	$ 6.7

We recognize revenue from sanofi-aventis, in connection with the companies' aflibercept collaboration, in accordance with Staff Accounting Bulletin No. 104, *Revenue Recognition* (SAB 104) and FASB Emerging Issues Task Force Issue No. 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables* (EITF 00-21). We earn contract research and development revenue from sanofi-aventis which, as detailed below, consists partly of reimbursement for research and development expenses and partly of the recognition of revenue related to a total of $105.0 million of non-refundable, up-front payments received in 2003 and 2006. Non-refundable up-front license payments are recorded as deferred revenue and recognized over the period over which we are obligated to perform services. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances.

Sanofi-aventis Contract Research & Development Revenue *(In millions)*	Three months ended September 30, 2007	2006
Regeneron expense reimbursement	$ 7.0	$ 7.0
Recognition of deferred revenue related to up-front payments	2.2	3.0
Total	$ 9.2	$ 10.0

Recognition of deferred revenue related to sanofi-aventis' up-front payments decreased in the third quarter of 2007 from the same period in 2006, due to an extension of the estimated performance period over which this deferred revenue is being recognized. As of September 30, 2007, $63.2 million of the original $105.0 million of up-front payments was deferred and will be recognized as revenue in future periods.

Other contract research and development revenue includes $2.2 million and $0.1 million in the third quarters of 2007 and 2006, respectively, recognized in connection with our five-year grant from the National Institutes of Health (NIH), which we were awarded in September 2006 as part of the NIH's Knockout Mouse Project.

Contract manufacturing revenue for the third quarter of 2006 related to our long-term agreement with Merck & Co., Inc., which expired in October 2006, to manufacture a vaccine intermediate at our Rensselaer, New York facility. Revenue and the related manufacturing

expense were recognized as product was shipped, after acceptance by Merck. Included in contract manufacturing revenue in the third quarter of 2006 was $0.4 million of deferred revenue associated with capital improvement reimbursements paid by Merck prior to commencement of production. We do not expect to receive any further contract manufacturing revenue from Merck.

In connection with our license agreement with AstraZeneca, as described above, the $20.0 million non-refundable up-front payment, which we received in February 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. In connection with our license agreement with Astellas, as described above, the $20.0 million non-refundable up-front payment, which we received in April 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. In the third quarter of 2007, we recognized $10.0 million of technology licensing revenue related to these agreements.

Expenses:

Total operating expenses increased to $61.0 million in the third quarter of 2007 from $43.9 million in the same period of 2006. Our average employee headcount in the third quarter of 2007 increased to 639 from 557 in the third quarter of 2006, primarily to support our expanded development programs for the VEGF Trap-Eye and rilonacept, and our plans to move our first antibody candidate into clinical trials. Operating expenses in the third quarter of 2007 and 2006 include a total of $7.0 million and $4.7 million, respectively, of non-cash compensation expense related to employee stock option awards (Stock Option Expense), as detailed below:

	For the three months ended September 30, 2007		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 47.6	$ 4.1	$ 51.7
General and administrative	6.4	2.9	9.3
Total operating expenses	$ 54.0	$ 7.0	$ 61.0

	For the three months ended September 30, 2006		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 32.1	$ 2.7	$ 34.8
Contract manufacturing	3.0	0.1	3.1
General and administrative	4.1	1.9	6.0
Total operating expenses	$ 39.2	$ 4.7	$ 43.9

The increase in total Stock Option Expense in the third quarter of 2007 was primarily due to the higher fair market value of our Common Stock on the date of our annual employee option grants made in December 2006 in comparison to the fair market value of our Common Stock on the dates of annual employee option grants made in recent prior years.

Research and Development Expenses:

Research and development expenses increased to $51.7 million in the third quarter of 2007 from $34.8 million in the same period of 2006. The following table summarizes the major

categories of our research and development expenses for the three months ended September 30, 2007 and 2006:

(In millions) Research and development expenses	Three months ended September 30, 2007	2006	Increase
Payroll and benefits (1)	$ 15.2	$ 11.0	$ 4.2
Clinical trial expenses	12.9	3.1	9.8
Clinical manufacturing costs (2)	11.9	10.0	1.9
Research and preclinical development costs	5.8	5.5	0.3
Occupancy and other operating costs	5.9	5.2	0.7
Total research and development	$ 51.7	$ 34.8	$ 16.9

(1) Includes $3.4 million and $2.3 million of Stock Option Expense for the three months ended September 30, 2007 and 2006, respectively.

(2) Represents the full cost of manufacturing drug for use in research, preclinical development, and clinical trials, including related payroll and benefits, Stock Option Expense, manufacturing materials and supplies, depreciation, and occupancy costs of our Rensselaer manufacturing facility. Includes $0.7 million and $0.5 million of Stock Option Expense for the three months ended September 30, 2007 and 2006, respectively.

Payroll and benefits increased primarily due to higher compensation expense due, in part, to the increase in employee headcount, as described above and annual salary increases effective January 1, 2007, and higher Stock Option Expense, as described above. Clinical trial expenses increased due primarily to (i) higher costs related to our ongoing Phase 1 and 2 studies of the VEGF Trap-Eye in wet AMD, (ii) costs related to our Phase 3 study of the VEGF Trap-Eye in wet AMD, which we initiated in the third quarter of 2007, and (iii) higher rilonacept costs. Clinical manufacturing costs increased primarily due to higher costs related to manufacturing rilonacept and preclinical and clinical supplies of our first antibody drug candidate. Research and preclinical development costs increased primarily due to higher costs related to our human monoclonal antibody programs and utilization of our proprietary technology platforms, such as for our NIH grant, as described above. Occupancy and other operating costs increased primarily as a result of higher facility-related and maintenance costs.

We budget our research and development costs by expense category, rather than by project. We also prepare estimates of research and development costs for projects in clinical development, which include direct costs and allocations of certain costs such as indirect labor, non-cash stock-based employee compensation expense related to stock option awards, and manufacturing and other costs related to activities that benefit multiple projects. Our estimates of research and development costs for clinical development programs are shown below:

(In millions) Project Costs	Three months ended September 30, 2007	2006	Increase (Decrease)
Rilonacept	$ 12.9	$ 7.7	$ 5.2
Aflibercept (VEGF Trap) – Oncology	5.5	5.5	
VEGF Trap- Eye	14.1	5.8	8.3
Other research programs & unallocated costs	19.2	15.8	3.4
Total research and development expenses	$ 51.7	$ 34.8	$ 16.9

Drug development and approval in the United States is a multi-step process regulated by the FDA. The process begins with discovery and preclinical evaluation, leading up to the submission of an IND to the FDA which, if successful, allows the opportunity for study in

humans, or clinical study, of the potential new drug. Clinical development typically involves three phases of study: Phase 1, 2 and 3. The most significant costs in clinical development are in Phase 3 clinical trials, as they tend to be the longest and largest studies in the drug development process. Following successful completion of Phase 3 clinical trials for a biological product, a biologics license application (or BLA) must be submitted to, and accepted by, the FDA, and the FDA must approve the BLA prior to commercialization of the drug. It is not uncommon for the FDA to request additional data following its review of a BLA, which can significantly increase the drug development timeline and expenses. We may elect either on our own, or at the request of the FDA, to conduct further studies that are referred to as Phase 3B and 4 studies. Phase 3B studies are initiated and either completed or substantially completed while the BLA is under FDA review. These studies are conducted under an IND. Phase 4 studies, also referred to as post-marketing studies, are studies that are initiated and conducted after the FDA has approved a product for marketing. In addition, as discovery research, preclinical development, and clinical programs progress, opportunities to expand development of drug candidates into new disease indications can emerge. We may elect to add such new disease indications to our development efforts (with the approval of our collaborator for joint development programs), thereby extending the period in which we will be developing a product. For example, we, and our collaborators, where applicable, continue to explore further development of rilonacept, aflibercept, and the VEGF Trap-Eye in different disease indications.

There are numerous uncertainties associated with drug development, including uncertainties related to safety and efficacy data from each phase of drug development, uncertainties related to the enrollment and performance of clinical trials, changes in regulatory requirements, changes in the competitive landscape affecting a product candidate, and other risks and uncertainties described below in Item 1A, "Risk Factors" under "Risks Related to Development of Our Product Candidates," "Regulatory and Litigation Risks," and "Risks Related to Commercialization of Products." The lengthy process of seeking FDA approvals, and subsequent compliance with applicable statutes and regulations, require the expenditure of substantial resources. Any failure by us to obtain, or delay in obtaining, regulatory approvals could materially adversely affect our business.

For these reasons and due to the variability in the costs necessary to develop a product and the uncertainties related to future indications to be studied, the estimated cost and scope of the projects, and our ultimate ability to obtain governmental approval for commercialization, accurate and meaningful estimates of the total cost to bring our product candidates to market are not available. Similarly, we are currently unable to reasonably estimate if our product candidates will generate product revenues and material net cash inflows. In the second quarter of 2007, we submitted a BLA for our rilonacept for the treatment of CAPS, a group of rare genetic disorders. We cannot predict whether or when the commercialization of rilonacept in CAPS will result in a material net cash inflow to us.

Contract Manufacturing Expenses:

Contract manufacturing expenses decreased in the third quarter of 2007 compared to the same period of 2006 due to the expiration of our manufacturing agreement with Merck in October 2006.

General and Administrative Expenses:

General and administrative expenses increased to $9.3 million in the third quarter of 2007 from $6.0 million in the same period of 2006 primarily due to (i) higher Stock Option Expense, as described above, (ii) higher compensation expense due, in part, to increases in administrative headcount in 2007 to support our expanded research and development activities and annual salary increases effective January 1, 2007, (iii) higher recruitment and related costs associated with expanding our headcount in 2007, (iv) higher fees for consultants and other professional services on various corporate matters, (v) marketing research and related expenses incurred in 2007 in connection with our rilonacept and VEGF Trap-Eye programs, and (vi) higher administrative facility and occupancy costs.

Other Income and Expense:

Investment income increased to $5.8 million in the third quarter of 2007 from $3.9 million in the same period of 2006 resulting primarily from higher balances of cash and marketable securities (due, in part, to the up-front payment received from Bayer HealthCare in October 2006, as described above, and the receipt of net proceeds from the November 2006 public offering of our Common Stock). This increase was partly offset by a $0.8 million charge in the third quarter of 2007 related to marketable securities which we considered to be other than temporarily impaired. Interest expense was $3.0 million in the third quarter of 2007 and 2006. Interest expense is attributable primarily to $200.0 million of convertible notes issued in October 2001, which mature in October 2008 and bear interest at 5.5% per annum.

Nine Months Ended September 30, 2007 and 2006

Net Loss:

Regeneron reported a net loss of $92.5 million, or $1.40 per share (basic and diluted), for the first nine months of 2007 compared to a net loss of $71.4 million, or $1.25 per share (basic and diluted), for the same period of 2006.

Revenues:

Revenues for the nine months ended September 30, 2007 and 2006 consist of the following:

(In millions)	2007	2006	Increase (Decrease)
Contract research & development revenue			
The sanofi-aventis Group	$ 34.5	$ 38.7	$ (4.2)
Other	7.4	2.3	5.1
Total contract research & development revenue	41.9	41.0	0.9
Contract manufacturing revenue		12.1	(12.1)
Technology licensing revenue	18.4		18.4
Total revenue	$ 60.3	$ 53.1	$ 7.2

We recognize revenue from sanofi-aventis, in connection with the companies' aflibercept collaboration, in accordance with SAB 104 and EITF 00-21. We earn contract research and development revenue from sanofi-aventis which, as detailed below, consists partly of reimbursement for research and development expenses and partly of the recognition of revenue

related to a total of $105.0 million of non-refundable, up-front payments received in 2003 and 2006. Non-refundable up-front license payments are recorded as deferred revenue and recognized over the period over which we are obligated to perform services. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances.

Sanofi-aventis Contract Research & Development Revenue *(In millions)*	**Nine months ended September 30, 2007**	**2006**
Regeneron expense reimbursement	$ 27.8	$ 29.6
Recognition of deferred revenue related to up-front payments	6.7	9.1
Total	$ 34.5	$ 38.7

Sanofi-aventis' reimbursement of Regeneron aflibercept expenses decreased in the first nine months of 2007 from the same period in 2006, primarily due to higher costs in 2006 related to the Company's manufacture of aflibercept clinical supplies. Recognition of deferred revenue related to sanofi-aventis' up-front payments decreased for the first nine months of 2007 from the same period in 2006, due to an extension of the estimated performance period over which this deferred revenue is being recognized. As of September 30, 2007, $63.2 million of the original $105.0 million of up-front payments was deferred and will be recognized as revenue in future periods.

Other contract research and development revenue includes $4.5 million and $0.1 million for the first nine months of 2007 and 2006, respectively, recognized in connection with our five-year grant from the NIH, which we were awarded in September 2006 as part of the NIH's Knockout Mouse Project.

Contract manufacturing revenue for the first nine months of 2006 related to our long-term manufacturing agreement with Merck, which expired in October 2006. Revenue and the related manufacturing expense were recognized as product was shipped, after acceptance by Merck. Included in contract manufacturing revenue in the third quarter of 2006 was $1.2 million of deferred revenue associated with capital improvement reimbursements paid by Merck prior to commencement of production. We do not expect to receive any further contract manufacturing revenue from Merck.

In connection with our license agreement with AstraZeneca, as described above, the $20.0 million non-refundable up-front payment, which we received in February 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. In connection with our license agreement with Astellas, as described above, the $20.0 million non-refundable up-front payment, which we received in April 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. In the first nine months of 2007, we recognized $18.4 million of technology licensing revenue related to these agreements.

Expenses:

Total operating expenses increased to $163.2 million in the first nine months of 2007 from $127.3 million in the same period of 2006. Our average employee headcount in the first nine months of 2007 increased to 614 from 574 in the first nine months of 2006, primarily to support our expanded development programs for the VEGF Trap-Eye and rilonacept and our plans to

move our first antibody candidate into clinical trials. Operating expenses for the first nine months of 2007 and 2006 include a total of $20.5 million and $13.2 million, respectively, of Stock Option Expense, as detailed below:

	For the nine months ended September 30, 2007		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 124.8	$ 12.0	$ 136.8
General and administrative	17.9	8.5	26.4
Total operating expenses	$ 142.7	$ 20.5	$ 163.2

	For the nine months ended September 30, 2006		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 94.0	$ 7.3	$ 101.3
Contract manufacturing	7.4	0.3	7.7
General and administrative	12.7	5.6	18.3
Total operating expenses	$ 114.1	$ 13.2	$ 127.3

The increase in total Stock Option Expense in the first nine months of 2007 was primarily due to the higher fair market value of our Common Stock on the date of our annual employee option grants made in December 2006 in comparison to the fair market value of our Common Stock on the dates of annual employee option grants made in recent prior years.

Research and Development Expenses:

Research and development expenses increased to $136.8 million in the first nine months of 2007 from $101.3 million in the same period of 2006. The following table summarizes the major categories of our research and development expenses for the nine months ended September 30, 2007 and 2006:

	Nine months ended September 30,		
(In millions) Research and development expenses	2007	2006	Increase
Payroll and benefits (1)	$ 43.3	$ 32.7	$ 10.6
Clinical trial expenses	24.8	11.0	13.8
Clinical manufacturing costs (2)	33.8	28.3	5.5
Research and preclinical development costs	17.9	13.3	4.6
Occupancy and other operating costs	17.0	16.0	1.0
Total research and development	$ 136.8	$ 101.3	$ 35.5

(1) Includes $9.8 million and $6.1 million of Stock Option Expense for the nine months ended September 30, 2007 and 2006, respectively.

(2) Represents the full cost of manufacturing drug for use in research, preclinical development, and clinical trials, including related payroll and benefits, Stock Option Expense, manufacturing materials and supplies, depreciation, and occupancy costs of our Rensselaer manufacturing facility. Includes $2.2 million and $1.2 million of Stock Option Expense for the nine months ended September 30, 2007 and 2006, respectively.

Payroll and benefits increased primarily due to higher compensation expense due, in part, to the increase in employee headcount, as described above and annual salary increases effective January 1, 2007, and higher Stock Option Expense, as described above. Clinical trial expenses

increased due primarily to (i) higher costs related to our ongoing Phase 1 and 2 studies of the VEGF Trap-Eye in wet AMD, (ii) costs related to our Phase 3 study of the VEGF Trap-Eye in wet AMD, which we initiated in the third quarter of 2007, and (iii) higher rilonacept costs. Clinical manufacturing costs increased due primarily to higher costs related to manufacturing rilonacept and preclinical and clinical supplies of our first antibody drug candidate, which were partly offset by lower costs related to manufacturing VEGF Trap. Research and preclinical development costs increased primarily due to higher costs related to our human monoclonal antibody programs and utilization of our proprietary technology platforms, such as for our NIH grant, as described above. Occupancy and other operating costs increased primarily as a result of higher facility-related and maintenance costs.

We budget our research and development costs by expense category, rather than by project. We also prepare estimates of research and development cost for projects in clinical development, which include direct costs and allocations of certain costs such as indirect labor, non-cash stock-based employee compensation expense related to stock option awards, and manufacturing and other costs related to activities that benefit multiple projects. Our estimates of research and development costs for clinical development programs are shown below:

(In millions)	Nine months ended September 30,		
Project Costs	**2007**	**2006**	**Increase (Decrease)**
Rilonacept	$ 28.7	$ 22.0	$ 6.7
Aflibercept (VEGF Trap) – Oncology	23.3	24.8	(1.5)
VEGF Trap- Eye	28.3	13.7	14.6
Other research programs & unallocated costs	56.5	40.8	15.7
Total research and development expenses	$ 136.8	$ 101.3	$ 35.5

For the reasons described above under "Research and Development Expenses" for the three months ended September 30, 2007 and 2006, and due to the variability in the costs necessary to develop a product and the uncertainties related to future indications to be studied, the estimated cost and scope of the projects, and our ultimate ability to obtain governmental approval for commercialization, accurate and meaningful estimates of the total cost to bring our product candidates to market are not available. Similarly, we are currently unable to reasonably estimate if our product candidates will generate product revenues and material net cash inflows.

Contract Manufacturing Expenses:

Contract manufacturing expenses decreased in the first nine months of 2007 compared to the same period of 2006 due to the expiration of our manufacturing agreement with Merck in October 2006.

General and Administrative Expenses:

General and administrative expenses increased to $26.4 million in the first nine months of 2007 from $18.3 million in the same period of 2006 primarily due to (i) higher Stock Option Expense, as described above, (ii) higher compensation expense due, in part, to increases in administrative headcount in 2007 to support our expanded research and development activities and annual salary increases effective January 1, 2007, (iii) higher recruitment and related costs

associated with expanding our headcount in 2007, (iv) higher fees for consultants and other professional services on various corporate matters, and (v) marketing research and related expenses incurred in 2007 in connection with our rilonacept and VEGF Trap-Eye programs.

Other Income and Expense:

Investment income increased to $19.4 million in the first nine months of 2007 from $11.0 million in the same period of 2006 resulting primarily from higher balances of cash and marketable securities (due, in part, to the up-front payment received from Bayer HealthCare in October 2006, as described above, and the receipt of net proceeds from the November 2006 public offering of our Common Stock). This increase was partly offset by a $0.8 million charge in the first nine months of 2007 related to marketable securities which, during the third quarter of 2007, we considered to be other than temporarily impaired. Interest expense was $9.0 million in first nine months of 2007 and 2006. Interest expense is attributable primarily to $200.0 million of convertible notes issued in October 2001, which mature in October 2008 and bear interest at 5.5% per annum.

Liquidity and Capital Resources

Since our inception in 1988, we have financed our operations primarily through offerings of our equity securities, a private placement of convertible debt, payments earned under our past and present research and development and contract manufacturing agreements, including our agreements with sanofi-aventis, Bayer HealthCare, and Merck, and investment income.

Nine Months Ended September 30, 2007 and 2006

At September 30, 2007, we had $497.3 million in cash, cash equivalents, restricted cash, and marketable securities, compared with $522.9 million at December 31, 2006. In connection with our new non-exclusive license agreements with AstraZeneca and Astellas, as described above, AstraZeneca and Astellas each made an up-front payment to us of $20.0 million in February and April 2007, respectively. In the third quarter of 2007, the Company received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in wet AMD.

Cash Used in Operations:

Net cash used in operations was $23.4 million in the first nine months of 2007, compared to $30.2 million in the first nine months of 2006. Our net losses of $92.5 million in the first nine months of 2007 and $71.4 million in the first nine months of 2006 included $20.5 million and $13.5 million, respectively, of non-cash stock-based employee compensation costs, of which $20.5 million and $13.2 million, respectively, represented Stock Option Expense and, in the first nine months of 2006, $0.3 million represented non-cash compensation expense from Restricted Stock awards. At September 30, 2007, our deferred revenue balances increased by $46.8 million, compared to year end 2006, due, in part, to the unrecognized balances of the two $20.0 million up-front payments received from each of AstraZeneca and Astellas, as described above. In addition, for the first nine months of 2007, the $20.0 million development milestone payment received from Bayer HealthCare in August 2007 and reimbursements from Bayer HealthCare of our 2007 VEGF Trap-Eye development expenses, totaling $12.9 million, have been fully

deferred and included in deferred revenue for financial statement purposes, as discussed above. At September 30, 2006, accounts receivable balances decreased by $28.6 million, compared to year end 2005, primarily due to the January 2006 receipt of a $25.0 million up-front payment from sanofi-aventis, which was receivable at December 31, 2005, in connection with an amendment to our collaboration agreement to include Japan. Also, our deferred revenue balances at September 30, 2006 decreased by $12.5 million, compared to year end 2005, due primarily to the revenue recognition of $9.1 million of deferred revenue related to up-front payments from sanofi-aventis during the first nine months of 2006. The majority of our cash expenditures in both the first nine months of 2007 and 2006 were to fund research and development, primarily related to our clinical programs and, in the first nine months of 2007, our preclinical human monoclonal antibody programs.

Cash (Used in) Provided by Investing Activities:

Net cash used in investing activities was $122.2 million in the first nine months of 2007 compared to net cash provided by investing activities of $8.1 million in the same period of 2006, due primarily to an increase in purchases of marketable securities net of sales or maturities. In the first nine months of 2007, purchases of marketable securities exceeded sales or maturities by $114.5 million, whereas in the first nine months of 2006, sales or maturies of marketable securities exceeded purchases by $9.7 million.

Cash Provided by Financing Activities:

Cash provided by financing activities, which in the first nine months of 2007 and 2006 is attributable primarily to the issuance of Common Stock in connection with exercises of employee stock options, decreased slightly to $5.2 million in the first nine months of 2007 from $5.3 million in the same period in 2006.

License Agreements with AstraZeneca and Astellas:

Under these non-exclusive license agreements, AstraZeneca and Astellas each made a $20.0 million non-refundable, up-front payment to us in February and April 2007, respectively. AstraZeneca and Astellas also will each make up to five additional annual payments of $20.0 million, subject to each licensee's ability to terminate its license agreement with us after making the first three additional payments or earlier if the technology does not meet minimum performance criteria.

Capital Expenditures:

Our additions to property, plant, and equipment totaled $7.9 million and $1.8 million for the first nine months of 2007 and 2006, respectively. During the remainder of 2007, we expect to incur approximately $10-12 million in capital expenditures (including approximately $9 million to purchase a facility in Rensselaer, New York, as described below) primarily to support our manufacturing, development, and research activities.

During the second quarter of 2007, we exercised a purchase option on a building in Rensselaer, totaling approximately 270,000 square feet, in which we leased approximately 75,000 square feet of manufacturing, office and warehouse space. We completed the purchase of

this property (land and building) in October 2007 at a cost of approximately $9 million, which is included in our anticipated capital expenditures for the remainder of 2007, as described above. The space that we do not occupy in this building is currently leased to another tenant.

Convertible Debt:

In 2001, we issued $200.0 million aggregate principal amount of convertible senior subordinated notes, which bear interest at 5.5% per annum, payable semi-annually, and mature in October 2008. The notes are convertible into shares of our Common Stock at a conversion price of approximately $30.25 per share, subject to adjustment in certain circumstances. If the price per share of our Common Stock is above $30.25 at maturity, we would expect the notes to convert into shares of Common Stock. Otherwise, we will be required to repay the $200.0 million aggregate principal amount of the notes or refinance the notes prior to maturity; however, we can provide no assurance that we will be able to successfully arrange such refinancing.

Amendment to Operating Lease – Tarrytown, New York Facilities:

We currently lease approximately 232,000 square feet of laboratory and office facilities in Tarrytown, New York. In December 2006, we entered into a new lease agreement to lease approximately 221,000 square feet of laboratory and office space at our current Tarrytown location, which includes approximately 27,000 square feet that would be retained from our current space and approximately 194,000 square feet in new facilities that are currently under construction and expected to be completed in mid-2009. In October 2007, we amended the December 2006 operating lease agreement to increase the amount of new space we will lease from approximately 194,000 square feet to approximately 230,000 square feet, for an amended total under the new lease of 257,000 square feet. The term of the lease is now expected to commence in mid-2008 and will expire approximately 16 years later. Other terms and conditions, as previously described in our Form 10-K for the year ended December 31, 2006, remain unchanged.

Funding Requirements:

We expect to continue to incur substantial funding requirements primarily for research and development activities (including preclinical and clinical testing). Before taking into account reimbursements from collaborators, we currently anticipate that approximately 55-65% of our expenditures for 2007 will be directed toward the preclinical and clinical development of product candidates, including rilonacept, aflibercept, VEGF Trap-Eye and monoclonal antibodies; approximately 10-15% of our expenditures for 2007 will be applied to our basic research activities and the continued development of our novel technology platforms; and the remainder of our expenditures for 2007 will be used for capital expenditures and general corporate purposes.

In connection with the amendment to our new operating lease agreement on our Tarrytown facilities and the purchase of a building in Rensselaer where we leased manufacturing, warehouse and office space, each as described above, our previously disclosed funding requirements for operating leases, as per our Form 10-K for the year ended December 31, 2006, will decrease for the two-year period beginning January 1, 2008 from $15.6 million to $13.9

million, increase for the two-year period beginning January 1, 2010 from $24.0 million to $28.6 million, and increase, in the aggregate, for fiscal years beginning January 1, 2012 and thereafter from $161.4 million to $204.2 million.

Under our collaboration with Bayer HealthCare, over the next several years we and Bayer HealthCare are sharing agreed upon VEGF Trap-Eye development expenses incurred by both companies, under a global development plan, as follows:

2007: Up to $50.0 million shared equally; we are solely responsible for up to the next $40.0 million; over $90.0 million shared equally. Through September 30, 2007, cumulative shared development expenses have exceeded $50.0 million.

2008: Up to $70.0 million shared equally, we are solely responsible for up to the next $30.0 million; over $100.0 million shared equally.

2009 and thereafter: All expenses shared equally.

In addition, under our collaboration agreements with sanofi-aventis and Bayer Healthcare, if the applicable collaboration becomes profitable, we have contingent contractual obligations to reimburse sanofi-aventis and Bayer Healthcare for 50% of agreed-upon development expenses incurred by sanofi-aventis and Bayer Healthcare, respectively. Profitability under each collaboration will be measured by calculating net sales less agreed-upon expenses. These reimbursements would be deducted from our share of the collaboration profits (and, for sanofi-aventis, royalties on product sales in Japan) otherwise payable to us unless we agree to reimburse these expenses at a faster rate at our option. Given the uncertainties related to drug development (including the development of the aflibercept in collaboration with sanofi-aventis and the VEGF Trap-Eye in collaboration with Bayer Healthcare) such as the variability in the length of time necessary to develop a product candidate and the ultimate ability to obtain governmental approval for commercialization, we are currently unable to reliably estimate if our collaborations with sanofi-aventis and Bayer Healthcare will become profitable.

The amount we need to fund operations will depend on various factors, including the status of competitive products, the success of our research and development programs, the potential future need to expand our professional and support staff and facilities, the status of patents and other intellectual property rights, the delay or failure of a clinical trial of any of our potential drug candidates, and the continuation, extent, and success of our collaborations with sanofi-aventis and Bayer HealthCare. Clinical trial costs are dependent, among other things, on the size and duration of trials, fees charged for services provided by clinical trial investigators and other third parties, the costs for manufacturing the product candidate for use in the trials, supplies, laboratory tests, and other expenses. The amount of funding that will be required for our clinical programs depends upon the results of our research and preclinical programs and early-stage clinical trials, regulatory requirements, the clinical trials underway plus additional clinical trials that we decide to initiate, and the various factors that affect the cost of each trial as described above. In the future, if we are able to successfully develop, market, and sell certain of our product candidates, we may be required to pay royalties or otherwise share the profits generated on such sales in connection with our collaboration and licensing agreements.

We expect that expenses related to the filing, prosecution, defense, and enforcement of patent and other intellectual property claims will continue to be substantial as a result of patent filings and prosecutions in the United States and foreign countries.

We believe that our existing capital resources will enable us to meet operating needs through at least early 2010, without taking into consideration the $200.0 million aggregate principal amount of convertible senior subordinated notes, which mature in October 2008. However, this is a forward-looking statement based on our current operating plan, and there may be a change in projected revenues or expenses that would lead to our capital being consumed significantly before such time. If there is insufficient capital to fund all of our planned operations and activities, we believe we would prioritize available capital to fund preclinical and clinical development of our product candidates. Other than a $1.6 million letter of credit issued to our landlord in connection with our new operating lease for facilities in Tarrytown, New York, we have no off-balance sheet arrangements. In addition, we do not guarantee the obligations of any other entity. As of September 30, 2007, we had no established banking arrangements through which we could obtain short-term financing or a line of credit. In the event we need additional financing for the operation of our business, we will consider collaborative arrangements and additional public or private financing, including additional equity financing. Factors influencing the availability of additional financing include our progress in product development, investor perception of our prospects, and the general condition of the financial markets. We may not be able to secure the necessary funding through new collaborative arrangements or additional public or private offerings. If we cannot raise adequate funds to satisfy our capital requirements, we may have to delay, scale back, or eliminate certain of our research and development activities or future operations. This could harm our business.

Critical Accounting Policies and Significant Judgments and Estimates

Revenue Recognition:

We recognize revenue from contract research and development and research progress payments in accordance with Staff Accounting Bulletin No. 104, *Revenue Recognition* (SAB 104) and Emerging Issues Task Force 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables* (EITF 00-21). We earn contract research and development revenue and research progress payments in connection with collaboration and other agreements to develop and commercialize product candidates and utilize our technology platforms. The terms of these agreements typically include non-refundable up-front licensing payments, research progress (milestone) payments, and payments for development activities. Non-refundable up-front license payments, where continuing involvement is required of us, are deferred and recognized over the related performance period. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances. Payments which are based on achieving a specific substantive performance milestone, involving a degree of risk, are recognized as revenue when the milestone is achieved and the related payment is due and non-refundable, provided there is no future service obligation associated with that milestone. Substantive performance milestones typically consist of significant achievements in the development life-cycle of the related product candidate, such as completion of clinical trials, filing for approval with regulatory agencies, and approvals by regulatory agencies. In determining whether a payment is deemed to be a substantive performance milestone, we take into consideration (i) the nature, timing, and value of significant achievements in the development life- cycle of the related development product candidate, (ii) the relative level of effort required to achieve the milestone, and (iii) the relative level of risk in achieving the milestone, taking into account the high degree of uncertainty in

successfully advancing product candidates in a drug development program and in ultimately attaining an approved drug product. Payments for achieving milestones which are not considered substantive are accounted for as license payments and recognized over the related performance period. Payments for development activities where Regeneron is not sharing costs are recognized as revenue as earned, over the period of effort. In addition, we record revenue in connection with a government research grant as we incur expenses related to the grant, subject to the grant's terms and annual funding approvals.

In connection with non-refundable licensing payments, our performance period estimates are principally based on projections of the scope, progress, and results of our research and development activities. Due to the variability in the scope of activities and length of time necessary to develop a drug product, changes to development plans as programs progress, and uncertainty in the ultimate requirements to obtain governmental approval for commercialization, revisions to performance period estimates are possible, and could result in material changes to the amount of revenue recognized each year in the future. In addition, performance periods may be extended if we and our collaborators decide to expand our clinical plans for a drug candidate into additional disease indications. Also, if a collaborator terminates an agreement in accordance with the terms of the agreement, we would recognize any unamortized remainder of an up-front payment at the time of the termination. For the year ended December 31, 2006, changes in estimates of our performance periods, including an extension of our estimated performance period for our collaboration with sanofi-aventis, did not have a material impact on contract research and development revenue that we recognized. In 2007, we currently expect to recognize at least $2.4 million lower contract research and development revenue, compared to amounts recognized in 2006, in connection with $105.0 million of non-refundable up-front payments previously received from sanofi-aventis, due to an extension of our estimated performance period.

As described above, we and Bayer HealthCare are currently formalizing our global development plans for the VEGF Trap-Eye in wet AMD and DME. Pending completion of these plans, all payments received or receivable from Bayer HealthCare through September 30, 2007 have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, we will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments from Bayer (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in our Statement of Operations. In the period when we commence recognizing previously deferred payments from Bayer HealthCare, we anticipate recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

Clinical Trial Expenses:

Clinical trial costs are a significant component of research and development expenses and include costs associated with third-party contractors. We outsource a substantial portion of our clinical trial activities, utilizing external entities such as contract research organizations, independent clinical investigators, and other third-party service providers to assist us with the execution of our clinical studies. For each clinical trial that we conduct, certain clinical trial costs are expensed immediately, while others are expensed over time based on the expected total number of patients in the trial, the rate at which patients enter the trial, and the period over which clinical investigators or contract research organizations are expected to provide services.

Clinical activities which relate principally to clinical sites and other administrative functions to manage our clinical trials are performed primarily by contract research organizations (CROs). CROs typically perform most of the start-up activities for our trials, including document preparation, site identification, screening and preparation, pre-study visits, training, and program management. On a budgeted basis, these start-up costs are typically 10% to 15% of the total contract value. On an actual basis, this percentage range can be significantly wider, as many of our contracts are either expanded or reduced in scope compared to the original budget, while start-up costs for the particular trial may not change materially. These start-up costs usually occur within a few months after the contract has been executed and are event driven in nature. The remaining activities and related costs, such as patient monitoring and administration, generally occur ratably throughout the life of the individual contract or study. In the event of early termination of a clinical trial, we accrue and recognize expenses in an amount based on our estimate of the remaining non-cancelable obligations associated with the winding down of the clinical trial and/or penalties.

For clinical study sites, where payments are made periodically on a per-patient basis to the institutions performing the clinical study, we accrue on an estimated cost-per-patient basis an expense based on subject enrollment and activity in each quarter. The amount of clinical study expense recognized in a quarter may vary from period to period based on the duration and progress of the study, the activities to be performed by the sites each quarter, the required level of patient enrollment, the rate at which patients actually enroll in and drop-out of the clinical study, and the number of sites involved in the study. Clinical trials that bear the greatest risk of change in estimates are typically those with a significant number of sites, require a large number of patients, have complex patient screening requirements, and span multiple years. During the course of a trial, we adjust our rate of clinical expense recognition if actual results differ from our estimates. Our estimates and assumptions for clinical expense recognition could differ significantly from our actual results, which could cause material increases or decreases in research and development expenses in future periods when the actual results become known. No material adjustments to our past clinical trial accrual estimates were made during the year ended December 31, 2006 or the nine months ended September 30, 2007.

During the three months ended September 30, 2007, there were no changes to any other "Critical Accounting Policies and Significant Judgments and Estimates" described in our Annual Report on Form 10-K for the year ended December 31, 2006.

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REGENERON
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September 28, 2008

VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting

Regression of total active lesion caused by wet AMD reported

SCOTTSDALE, Ariz., Sep 28, 2008 (BUSINESS WIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare AG announced that VEGF Trap-Eye achieved durable improvements in visual acuity and in biologic measures of neovascular disease, including retinal thickness and active choroidal neovascularization lesion size, for up to one year in a Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD). The results were reported today in two oral presentations at the 2008 annual meeting of the Retina Society in Scottsdale, Arizona. Slides, including data reported at the presentations, are available on the Regeneron website (www.regeneron.com on the Presentations Page, under the Investor Relations section).

In this double-masked Phase 2 trial, patients were initially treated with either fixed monthly or quarterly dosing for 12 weeks and then continued to receive treatment for another 40 weeks on a PRN (as needed) dosing schedule. Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline of 9.0 letters ($p<0.0001$ versus baseline) and 5.4 letters ($p<0.085$ versus baseline), respectively, at the end of one year. The proportion of patients with vision of 20/40 or better (part of the legal minimum requirement for an unrestricted driver's license in the U.S.) increased from 23 percent at baseline to 45 percent at week 52 in patients initially treated with 2.0 mg monthly and from 16 percent at baseline to 47 percent at week 52 in patients initially treated with 0.5 mg monthly. During the week 12 to week 52 PRN dosing period, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.

Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 mg for 12 weeks followed by PRN dosing also achieved mean decreases in retinal thickness versus baseline of 143 microns ($p<0.0001$ versus baseline) and 125 microns ($p<0.0001$ versus baseline) at week 52, respectively.

While PRN dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity and retinal thickness versus baseline at week 52, the results generally were not as robust as those obtained with initial fixed monthly dosing.

"Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD, and improvement in visual acuity is now feasible in most patients. The biggest challenge we have is that with our current drugs, the majority of patients need frequent injections into their eye to maintain their visual acuity gains," stated David M. Brown, M.D., a study investigator and a retinal specialist at The Methodist Hospital in Houston. "These study results reinforce our interest in further exploring whether continued administration of VEGF Trap-Eye on an as-needed basis after an initial period of fixed dosing can maintain a durability of effect over time in controlled Phase 3 clinical studies."

In this Phase 2 study VEGF Trap-Eye was also associated with a reduction in the size of the total active choroidal neovascular membrane (CNV), the active lesion that is the underlying cause of vision loss in patients with wet AMD. Patients initially receiving either a 2.0 mg or 0.5 mg monthly fixed dose of VEGF Trap-Eye for 12 weeks followed by PRN dosing experienced statistically significant 3.41 mm(2) and 1.42 mm(2) reductions in mean CNV size at 48 weeks (the final one-year analysis from the independent reading center) versus baseline, respectively. Patients in the 2.0 mg monthly cohort also achieved a statistically significant 1.75 mm(2) reduction in total lesion size. A reduction in total lesion size was not seen in the cohort initially dosed with 0.5 mg monthly.

"Progression of the active CNV lesion and resulting vision impairment are inevitable consequences of untreated wet AMD. The reduction in total active CNV lesion size achieved with VEGF Trap-Eye treatment in this Phase 2 clinical study could potentially translate into clinically meaningful outcomes in the larger, controlled Phase 3 studies that are underway," stated Jason Slakter, M.D., head of the independent reading center for the study and a Clinical Professor of Ophthalmology, New York University School of Medicine, New York.

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

"These study results confirm the rationale for our Phase 3 clinical program for VEGF Trap-Eye in wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "These trials are designed to optimize improvement in visual acuity with fixed-dosing regimens of either every 4 weeks or every 8 weeks for one year and then study how these vision improvements can be maintained with as-needed dosing in the second year."

About the Phase 2 Study in Wet AMD

In the double-masked, prospective, randomized, multi-center Phase 2 trial, 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity. The primary endpoint results from the fixed dosing period were presented at the 2007 Retina Society conference in September 2007. Week 32 results were presented at the 2008 Association for Research in Vision and Ophthalmology annual meeting in April 2008.

About the Phase 3 Program in Wet AMD

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

About VEGF Trap-Eye

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

About Wet AMD

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

About Regeneron Pharmaceuticals, Inc.

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

Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital,

the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2007 and Form 10-Q for the quarter ended June 30, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

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REVIEW ARTICLE

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Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration

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Contents

Abstract

Angiogenesis, the process by which new vessels are created from pre-existing vasculature, has become the subject of intense research in recent years. Increased rates of angiogenesis are associated with several disease states, including cancer, age-related macular degeneration (AMD), psoriasis, rheumatoid arthritis, and diabetic retinopathy. Vascular endothelial growth factor (VEGF) is an important modulator of angiogenesis, and has been implicated in the pathology of a number of conditions, including AMD, diabetic retinopathy, and cancer. AMD is a progressive disease of the macula and the third major cause of blindness worldwide. If not treated appropriately, AMD can progress to involve both eyes. Until recently, the treatment options for AMD have been limited, with photodynamic therapy (PDT) the mainstay of treatment. Although PDT is effective at slowing disease progression, it rarely results in improved vision. Several therapies have been or are now being developed for neovascular AMD, with the goal of inhibiting VEGF. These VEGF inhibitors include the RNA aptamer pegaptanib, partial and full-length antibodies ranibizumab and bevacizumab, the VEGF receptor decoy aflibercept, small interfering RNA-based therapies bevasiranib and AGN 211745, sirolimus, and tyrosine kinase inhibitors, including vatalanib, pazopanib, TG 100801, TG 101095, AG 013958, and AL 39324. At present, established therapies have met with great success in reducing the vision loss associated with neovascular AMD, whereas those still under investigation offer the potential for further advances. In AMD patients, these therapies slow the rate of

vision loss and in some cases increase visual acuity. Although VEGF-inhibitor therapies are a milestone in the treatment of these disease states, several concerns need to be addressed before their impact can be fully realized.

Angiogenesis is a term used to describe the formation of new blood vessels from the pre-existing vasculature. This process is critical for several normal physiologic functions, including the development of embryos, wound healing, the female reproductive cycle, and collateral vascular generation in the myocardium. However, aberrant angiogenesis has been implicated in the progression of several disease states, including cancer, macular degeneration, diabetic retinopathy, rheumatoid arthritis, and psoriasis.

Under normal physiologic conditions, the process of angiogenesis is well controlled, reflecting a perfect balance of endogenous angiogenic growth factors and suppressors. When angiogenic growth factors outnumber angiogenesis inhibitors, the balance shifts in favor of angiogenesis, a process termed the 'angiogenic switch.'[1] Rigorous research in the field of angiogenesis has led to the identification of many regulators involved in this process. Angiogenesis is driven by the production of proangiogenic growth factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-8, placental-like growth factor (PLGF), transforming growth factor-β (TGFβ), nitric oxide synthetase, angiopoietin, platelet-derived growth factor (PDGF), pleiotrophin, and several others.[2] Activation by VEGF and other proangiogenic factors causes endothelial cells to release proteases that degrade the basement membrane. This allows endothelial cells to escape from the original vessel walls, proliferate, and extend toward the source of the angiogenic stimulus, using integrins to mediate cell adhesion.[1,3] Angiogenesis can also be promoted by a deficiency in endogenous angiogenesis inhibitors, which include angiostatin, canstatin, endostatin, various heparinases, interferon-α, -β, -γ, thrombospondin, and others.[3]

The main purpose of this review is to summarize the physiologic role of VEGF, particularly within the eye, and its role in the development of age-related macular degeneration (AMD), and to highlight both the benefits and potential adverse effects of anti-VEGF-based therapy.

1. Pathologic Angiogenesis and Anti-Angiogensis Therapies

Research shows that angiogenesis accompanies the progression of chronic inflammation. VEGF is over-expressed in a number of proinflammatory conditions, including psoriasis and rheumatoid arthritis.[4,5] During tumorigenesis, lack of oxygen and other essential nutrients restricts tumor growth to 1–2 mm.[3,6] In order to grow beyond this size, tumor cells must induce angiogenesis by secreting angiogenic growth factors. This angiogenic vascularization not only allows the tumor to grow, but also increases the rate of metastasis. Vessels formed by uncontrolled and unregulated angiogenesis are drastically different from those of the normal vasculature, being characterized by chaotic branching, hypoxia, and increased interstitial pressure. These irregularities might also hinder the ability of chemotherapeutic agents to reach desired drug concentrations within the tumor vasculature. Thus, VEGF has become an attractive target of investigation for the treatment of various types of cancer.

A wide range of therapies designed to inhibit angiogenesis have been developed and many more are currently under investigation. Angiogenesis inhibitors are typically divided into two categories: direct or indirect. Direct angiogenesis inhibitors are designed to target endothelial cells and prevent their proliferation. Indirect therapies target proangiogenic growth factors or their receptors. In general, endothelial cells are viewed as an excellent target for therapy because they are genetically more stable than cancer cells. In fact, it has been postulated that this stability reduces the likelihood of rapid mutation and acquired drug resistance.[7] Recent studies suggest, however, that tumor endothelial cells carry genetic anomalies that may confer drug resistance.[8,9] Interestingly, it has been suggested that traditional therapies, such as radiation therapy, may actually work in part by targeting genomically stable endothelial cells, as these endothelial cells are still proliferating at a higher than normal rate.[8,9]

Indirect inhibition of angiogenesis can be further divided into two categories, those that amplify the effects of angiogenic inhibitors and activate their associated pathways, or those that inhibit the activation of proangiogenic pathways. Currently, there are a number of angiogenic regulators and their receptors under investigation. For example, a recent phase II trial investigating the use of a TGFβ antisense vaccine, belagenpumatucel-L (Lucanix®), in patients with non-small cell lung cancer reported favorable results.[10] Focusing on 61 assessable patients with late-stage (IIIB and IV) disease, a 15% partial response rate was achieved and the estimated probabilities of

surviving 1 and 2 years were 68% and 52%, respectively. These results were favorable as compared with historic controls, and no significant adverse events were observed. Another promising experimental strategy targeting TGFβ employs the use of a soluble TGFβ receptor, which specifically inhibits TGFβ-1 and TGFβ-3.[11,12]

2. Pathogenesis of Age-Related Macular Degeneration (AMD)

AMD is a multifaceted disease characterized by early subclinical changes at the choroidea-retinal pigment epithelium interface. Both the causal and formal pathogenesis of the disease is still puzzling. The disease can progress into two distinct late forms, 'geographic atrophy' and 'choroidal neovascularization;' the underlying mechanism of this differential progression remains unknown.[13] Late changes are usually responsible for the dramatic loss in central function that has a devastating effect on quality of life. In industrialized countries, the disease is a major cause of visual disability among persons over 60 years of age. Due to demographic right-shift and increased life expectancy, AMD is not only a medical problem, but also has pronounced socio-economic effects. In the last few decades, treatment modalities have been based on the destruction or surgical removal of the neovascular complex. At present, however, the philosophical approach to treatment has changed to one of modifying disease pathology. AMD is a progressive disease that affects the central portion of the retina (the macula). In the earliest stage, deposits called drusen form in the area between the retinal pigment epithelium and the underlying choroid. Advanced AMD, which is responsible for profound vision loss, has two forms: dry and wet. The dry form of advanced AMD results from atrophy of the retinal pigment epithelial layer below the retina. There is currently no treatment option for this type of AMD. In wet AMD (neovascular AMD), neovascularization of the choroid occurs, resulting in blood and protein leakage. The seepage and scarring from these blood vessels eventually cause irreversible damage to the photoreceptors and can lead to vision loss.[13] Angiogenic growth factors, particularly VEGF, have been shown to be elevated in patients with the wet form of AMD and play a key role in the neovascularization process.[14]

Intelligent targeting of the relevant factors and pathways involved in AMD should stop disease progression, reduce complications and improve vision. The first step into this new era has been accomplished with the introduction of anti-angiogenic agents. These new agents act either directly on VEGF or indirectly on the VEGF signaling cascade. It is important to bear in mind, however, that while VEGF contributes at a fundamental level to neovascular processes, it also acts in other physiologic pathways as well.[3]

3. Biologic Activities of VEGF

VEGF belongs to a family of dimeric glycoproteins within the superfamily of PDGFs. While VEGF, also known as VEGF-A, is the most comprehensively studied, other members of this family include VEGF-B, VEGF-C, VEGF-D, and PLGF.[15,16] VEGF-A has several isoforms ($VEGF_{121}$, $VEGF_{121}b$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$) that arise from alternative splicing. Of these isoforms, $VEGF_{145}$ is the most abundant.[17] All VEGF ligands bind to tyrosine kinase receptors, causing the receptors to dimerize and autophosphorylate.[18] Upon binding to its receptor, VEGF initiates a cascade of signaling events that begins with auto-phosphorylation of both receptor kinases, followed by activation of numerous downstream proteins, including phosphoinositide-3-kinase (PI3K), the Ras GTPase activating protein, Ras, mitogen-activated protein kinase (MAPK), and others.[19] VEGF-A binds to VEGF receptor (VEGFR)-1 (also known as fetal liver tyrosine kinase-1, or FLT1) and VEGFR-2 (also known as kinase insert domain receptor [KDR] or FLK1).[18] VEGFR-2 has a higher affinity for VEGF than VEGFR-1, and has been implicated in the potentiation of angiogenesis.[19] The function of VEGFR-1 is less well defined, but seems to include recruitment of monocytes.[19] VEGF-C and VEGF-D bind to a different receptor, VEGFR-3, which has been shown to mediate lymphangiogenesis.[16] VEGF promotes the growth, migration, and proliferation of endothelial cells.[20-22] In addition, VEGF induces vasodilatation and enhances endothelial cell survival.[20,21] These biologic activities occur in few physiologic processes outside wound healing and ovulation, making VEGF an attractive target for therapy.

4. Role of VEGF in AMD

VEGF is over-expressed in patients diagnosed with AMD. In a recent study designed to determine the effect of VEGF over-expression in retinal pigment epithelial cells, investigators injected a recombinant adenovirus vector expressing rat $VEGF_{164}$ into the sub-retinal space of the rat eye.[14] The expression of VEGF messenger RNA (mRNA) was increased in retinal pigment epithelial cells and blood vessels became leaky 10 days post-injection. By 80 days post-injection, new blood

vessels originating from the choriocapillarie were detected, ultimately leading to the formation of choroidal neovascular membranes and death of photoreceptor cells. This study demonstrated that over-expression of VEGF in retinal pigment epithelial cells can induce vascular leakage, new choroidal blood vessel growth, choroidal neovascularization, and neural retina degeneration in the rat eye.[14] This process mirrors the mechanism of vision loss in AMD, supporting the idea that VEGF over-expression plays a key role in AMD.

5. VEGF Inhibition in the Treatment of AMD

Approved therapeutic agents as well as those currently in development that target VEGF employ one of several mechanisms of action to inhibit the VEGF functional pathway. One approach involves the use of monoclonal antibodies (mAbs) to target either VEGF or its receptors. Soluble VEGFRs with high affinity for VEGF have also been designed that prevent VEGF binding to its receptor on endothelial cells. Various small-molecule tyrosine kinase inhibitors (TKIs) have been developed to specifically inhibit VEGFR tyrosine kinase activity. Two unique classes of drugs have emerged that target VEGF mRNA. The first is designed to target post-transcriptional modification of VEGF mRNA and prevent protein translation of VEGF;[23] the second involves the use of small interfering (si)RNA to prevent transcription of VEGF mRNA.[24]

5.1 Aptamer Therapy

Pegaptanib (Macugen®) is approved by the US FDA for the treatment of wet AMD. Pegaptanib is an aptamer, a short RNA oligonucleotide that assumes a specific three-dimensional shape and binds with high affinity to target molecules. Pegaptanib reduces neovascularization by inhibiting a specific isoform of VEGF, $VEGF_{165}$. Efficacy and safety analyses were recently reported in two randomized, sham-controlled, clinical trials.[25,26] The two combined trials, known as the VISION (VEGF Inhibition Study in Ocular Neovascularisation) study, enrolled 1186 patients. Patients received either an intraocular injection of pegaptanib or a similar sham injection every 6 weeks. Visual acuity (VA) was measured using Snellen eye charts, during which patients were asked to identify specific sized letters or lines at a set distance.[25,26]

The VISION study demonstrated a significant difference in loss of VA by 1 year in patients who received pegaptanib as compared with those who received sham injection (a loss of 7.93 letters for pegaptanib vs 15.05 letters for sham; $p < 0.0001$), which was maintained at 2 years.[25,26] The risk of severe loss of VA (loss of 30 letters or more) from baseline was 22% in the sham-injection group and 10% in the pegaptanib group ($p < 0.001$). In addition, patients in the sham group were more likely to lose three or more Snellen lines from their vision as compared with the pegaptanib group at 1 and 2 years ($p < 0.001$ and $p < 0.05$, respectively). These results indicate that pegaptanib is effective in reducing vision loss in patients with several types of AMD.[25,26]

A study on the cost effectiveness of pegaptanib was performed in 2005, from the perspective of the UK government.[26] The results showed that pegaptinib therapy had a mean incremental cost-effectiveness ratio of £8023 per vision year saved, well below the threshold of £20 000 per vision year saved. The therapy was deemed cost effective for the UK government.[26]

5.2 Monoclonal Antibody Therapy

The anti-VEGF mAb ranibizumab (Lucentis®) was approved for the treatment of wet AMD in the US in 2006. In a 2-year, phase III, randomized, double-blind, sham-controlled study, patients received either ranibizumab low dose ($n = 238$), ranibizumab high dose ($n = 240$), or a sham injection administered intravitreally once monthly in one eye for 2 years. The primary outcome of VA was assessed by determining the number of patients who lost fewer than 15 letters from baseline. Compared with the sham-injection group, significantly higher numbers of patients in the ranibizumab groups were more likely to lose fewer than 15 letters (94.5% for high-dose ranibizumab and 94.6% for low-dose ranibizumab vs 62.2% for sham injection; $p < 0.001$).[27] In fact, vision improvement was noted, with mean VA improving by about seven letters in the ranibizumab groups. By comparison, there was a decline of ten letters in the sham-injection group ($p < 0.001$). At the study conclusion, 26.1% and 33.3% of patients in the low- and high-dose ranibizumab groups, respectively, had a VA gain of 15 letters or more, compared with 3.8% of patients in the sham-injection group ($p < 0.001$).[27] These results were similar to and supported earlier phase I/II studies.[28]

Verteporfin photodynamic therapy (PDT) is indicated for wet, neovascular AMD. Prior to the advent of VEGF inhibitors, it was the treatment of choice for wet AMD. Recently, ranibizumab was compared with verteporfin PDT in a 2-year, randomized, double-blind, multicenter trial.[29] Patients received either low- or high-dose ranibizumab or verteporfin PDT. Those patients who received ranibizumab had significantly better VA, as indicated by more patients losing fewer than 15 letters on Snellen charts. Also, more patients in the ranibizumab group

gained 15 or more letters (35.7% in the low-dose and 40.3% in the high-dose ranibizumab groups) as compared with the verteporfin group (5.6%; $p < 0.001$). Severe loss of VA, indicated by a decline of 30 letters or more, occurred in 13.3% of patients receiving verteporfin as compared with none receiving ranibizumab ($p < 0.001$). Two cases of presumed endophthalmitis and one case of serious uveitis were reported in the high-dose ranibizumab group, while no such events occurred in the verteporfin or low-dose ranibizumab groups.[29]

More frequent administration (defined as <2 months mean inter-injection interval) of ranibizumab in the eye resulted in greater gain in VA (+2.3 lines at 6 months) than less frequent injections (+0.46 lines at 6 months; $p = 0.012$).[30] This study found that in a population of patients receiving as-needed injections of ranibizumab for exudative AMD, visual improvement was related to the frequency of injections received, but not to the resolution of fluid on optical coherence tomography. Thus, treatment with ranibizumab on a strictly as-needed basis may result in under-treatment and significantly less gain in VA.[30]

Bevacizumab is closely related to ranibizumab, differing in that it is a full-length humanized mAb against VEGF, whereas ranibizumab is an antigen binding fragment. Currently, bevacizumab is approved by the FDA for first-line treatment of patients with colon cancer, but it is also used on a large scale off-label for the treatment of exudative AMD.[31] An early, non-randomized trial of bevacizumab in patients with wet AMD showed highly significant improvement in vision (mean change in ETDRS [Early Treatment Diabetic Retinopathy Study] letters, + 10) at 4 and 8 weeks following intravitreal injection.[32] Several small, head-to-head, randomized controlled trials subsequently showed that intravitreal administration of bevacizumab was more efficacious than PDT in improving VA,[33-35] and the incidence of adverse effects was low. A recent meta-analysis of the effects of bevacizumab in exudative AMD found that changes in VA associated with bevacizumab were similar to ranibizumb (+5.9–9.8 and +8.6 ETDRS letters, respectively). A major advantage of bevacizumab is cost, which is approximately 1–5% of that associated with ranibizumab.[31] However, large-scale, randomized controlled trials are needed in order to establish the efficacy and safety of bevacizumab.

5.3 Other VEGF-Targeting Approaches in AMD

Several other therapies for AMD that target VEGF are currently being investigated in clinical trials. Aflibercept (VEGF Trap-Eye) is a receptor decoy that targets VEGF with higher affinity than ranibizumab and other currently available anti-VEGF therapies.[36,37] Aflibercept is being studied in phase II trials as an intravitreal injection, as well as in two phase III clinical trials (VIEW-1 and VIEW-2 [VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD]) comparing aflibercept to ranibizumab, which will provide important insight into the clinical applicability of this drug.[37]

Bevasiranib, the first small interfering RNA (siRNA) agent developed for the treatment of neovascular AMD that has shown clinical promise, has an acceptable safety profile supported by preclinical and clinical data.[38] Injected intravitreally, bevasiranib induces catalytic destruction of mRNA to silence gene expression, thereby targeting *de novo* production of VEGF.[38] Bevasiranib does not appear to affect existing VEGF levels, suggesting that there may be a synergistic effect of combining bevasiranib with other anti-VEGF treatments, such as ranibizumab. Other siRNA-based therapies, such as those designed to target VEGFRs (e.g. AGN 211745), are also being investigated. Recently, it was shown that administration of a siRNA targeting hypoxia-inducible factor (HIF)-1α results in marked decreases in VEGF at the mRNA and protein levels within the retinal pigment epithelium.[39] Antagonism of HIF-1α, however, may lead to the over-activation of alternate transcription factors and their respective target genes, leading to less effective inhibition of angiogenesis.[40] siRNA targeting of VEGF, on the other hand, has the advantage of decreasing the production of several clinically important angiogenic factors, thereby more effectively inhibiting angiogenesis.[40] Other potential therapies in development include pigment epithelium-derived factor-based therapies, nicotinic acetylcholine receptor antagonists, integrin antagonists, and sirolimus.

6. Combined Therapies in AMD

Anti-angiogenesis agents have largely supplanted PDT as a first-line therapy for exudative AMD. Clinical studies examining combination treatments in AMD provide strong evidence that PDT in combination with anti-angiogenesis agent(s) may be more effective than monotherapeutic approaches.[41] Available data suggest that PDT can potentially reduce the frequency with which intravitreal injections of anti-angiogenesis agents are required; anti-angiogenesis agents may in turn augment the activity of PDT by inhibiting the counterproductive upregulation of VEGF.[41]

The effect of combined PDT and intravitreal injection of ranibizumab was recently investigated in a pilot study in 28 patients with occult choroidal neo-vascularizaion (CNV) with recent disease progression ($n = 11$) and CNV due to AMD ($n = 17$).[42] An intravitreal injection of ranibizumab was

administered within 12–24 hours after standard PDT, followed by two additional injections of ranibizumab after 1 and 2 months. PDT in combination with intravitreal ranibizumab was well tolerated and effective, with stabilization of VA in 96% of patients. The combination of bevacizumab and low-dose PDT significantly reduced the number of bevacizumab treatments required over 6 months.[43] This particular study was powered to examine number of treatments, but not effects on VA; thus, further studies are required to explore visual outcomes.

A retrospective, case series database study (registry) assessed outcomes for patients with CNV due to AMD treated with verteprofin PDT and bevacizumab.[44] The study included 1196 patients with CNV due to AMD who were treated with one or more combination treatments of intravitreal bevacizumab 1.25 mg administered within 14 days of verteporfin PDT. Combination therapy with PDT and bevacizumab led to vision benefit for most patients, particularly those who were treatment naïve at baseline.[44] The number of re-treatments was lower than published reports with either treatment delivered as monotherapy. Randomized clinical trials are underway to confirm these findings.

Finally, the efficacy and safety of triple therapy consisting of single-session PDT, intravitreal bevacizumab, and intravitreal triamcinolone for the treatment of neovascular AMD was evaluated in patients with subfoveal CNV secondary to AMD.[45] This study concluded that single-session triple therapy might be a useful treatment option for neovascular AMD based on low retreatment rates, sustainable eradication of CNV, and achievement of visual gain. However, the risk and benefits of using intravitreal triamcinolone in addition to combined PDT and intravitreal bevacizumab warrant further evaluation.

7. Comparative Efficacy of Different Therapies in AMD

In a systematic review of pegaptanib and ranibizumab, it was shown that patients with AMD of any lesion type benefited from treatment with either agent on measures of VA as compared to sham and/or PDT treatment.[46] In addition, patients who continued treatment with either drug for up to 2 years appeared to maintain benefits. Cost-effectiveness analysis showed that the two drugs offer additional benefit over the comparators of usual care and PDT, but at increased cost.[46] The relative benefit of each therapy was less clear, due in part to the lack of data from direct comparison head-to-head trials.

The effects of different treatments on serious pigment epithelium detachment (PED) in AMD have been investigated.[47] Therapeutic results were significantly better in patients treated with bevacizumab and ranibizumab than in those treated with pegaptanib, or with a combination of PDT and intravitreal injection of triamcinolone acetonide. Even with treatment, tears of the retinal pigment epithelium or partial flattening of the PED always indicated a worse prognosis in eyes with exudative AMD than in eyes with CNV.[47]

A recent retrospective study compared the safety and efficacy of ranibizumab with bevacizumab in the treatment of patients with neovascular AMD.[48] Bevacizumab or ranibizumab treatment resulted in similar gains in VA and reductions in macular thickness, as documented each month following injection. Thus, intravitreal bevacizumab appears to be as safe and effective as intravitreal ranibizumab in the treatment of exudative AMD.[48] It is likely that a randomized controlled trial, if it can be done, will show that bevacizumab is equivalent to ranibizumab in terms of efficacy and safety.[31] In addition, there are currently no long-term results available to assess whether the effects of these therapies are long-lived or if alternative angiogenesis pathways eventually overcome VEGF inhibition, resulting in disease progression.

8. Anti-VEGF Therapies in Other Indications

Several novel classes of anti-angiogenesis targets are currently under investigation for the treatment of various cancers and deserve mention, as their use could potentially be expanded for ocular indications such as AMD.

8.1 Tyrosine Kinase Inhibition

One of the most intensely investigated therapeutic strategies is the use of inhibitors of the tyrosine kinase cascade downstream of the VEGFR to block the effects of VEGF. Therapies currently in development in this category include vatalanib, TG 100801, pazopanib, AG 013958, and AL 39324.

An oral, multi-targeted receptor TKI, sunitinib (SU11248), inhibits VEGFR-2, PDGF receptor (PDGFR), and FLT3, and has been shown to suppress leakage in an experimental mouse model of CNV caused by AMD.[49] Inhibition of these tyrosine kinase receptors also prevents tumor growth, pathologic angiogenesis, and metastatic progression of certain cancers.[50] In patients with gastrointestinal stromal tumors who had previously not responded to imatinib, sunitinib improved time to progression (TTP) and progression-free survival (PFS) as compared with placebo.[50] Sunitinib is currently approved by the FDA for gastrointestinal stromal tumors.

Sorafenib (Nexavar®, BAY 43-9006) is a TKI that inhibits tumor angiogenesis by blocking the activation of several tyrosine kinase receptors involved in neovascularization and tumor

progression, including VEGFR-2, VEGFR-3, PDGFR-B, FLT3, KIT, and p38-α (MAPK14).[51-53] Sorafenib also inhibits the activities of RAF1 and BRAF, which are involved in the regulation of endothelial apoptosis.[51] In phase III trials, oral sorafenib prolonged PFS as compared to placebo in patients with advanced clear-cell renal-cell carcinoma in whom first-line therapy had failed.[54] In addition, partial responses were significantly higher in the sorafenib group as compared with placebo. Treatment was associated with increased adverse events, including diarrhea, rash, fatigue, hand-foot skin reactions, hypertension, and cardiac ischemia. This study confirmed earlier phase II results showing that sorafenib significantly increased PFS in patients with advanced renal cell carcinoma.[55] Sorafenib is currently FDA approved for liver and renal cancer.

AEE 788 is potent combined inhibitor of epidermal growth factor receptor (EGFR) and VEGFR. *In vitro*, AE 788 effectively inhibits EGFR and VEGFR phosphorylation, exerts anti-proliferative effects in a range of EGFR- and ErbB2 (HER2)-overexpressing cell lines, and inhibits the proliferation of EGF- and VEGF-stimulated human umbilical vein endothelial cells.[56] *In vivo*, AEE 788 decreased tumor growth in several animal models of cancer, including tumors that overexpress EGFR and/or HER2.[56] Oral administration of AEE 788 resulted in high and persistent drug levels in tumor tissue, and inhibited VEGF-induced angiogenesis in a murine implant model.[56] AEE 788 is currently being studied in phase I clinical trials for cancer indications, and represents a potential candidate for ocular trials, pending satisfactory efficacy and safety data.

Axitinib (AG 013736) is an oral selective inhibitor of VEGFR-1, -2, and -3. In a phase II clinical trial of 52 patients diagnosed with metastatic renal-cell cancer who had experienced treatment failure with previous cytokine-based treatment regimes, axitinib was associated with two complete and 21 partial responses, with an objective response rate of 44.2% and a median response duration of 23.0 months.[57] The primary endpoint was objective response (based on RECIST [Response Evaluation Criteria in Solid Tumors]), and secondary endpoints were duration of response, TTP, overall survival, safety, pharmacokinetics, and patient-reported health-related quality of life. Treatment-related adverse events included diarrhea, hypertension, fatigue, nausea, and hoarseness. Overall, the results of this trial indicate that axitinib has clinical activity in patients with cytokine-refractory metastatic renal-cell cancer.

Cediranib (AZD 2171) is a highly potent ATP-competitive inhibitor of recombinant KDR tyrosine kinase activity *in vitro*. AZD 2171 inhibits VEGF-stimulated proliferation and KDR phosphorylation in human umbilical vein endothelial cells, and reduces vessel area, length, and branching in a fibroblast and endothelial cell model of vessel sprouting.[58] *In vivo*, AZD 2171 inhibits the growth of tumor xenografts in various mouse models of carcinogenesis, including colon, lung, prostate, breast, and ovary.[58] The safety and efficacy of AZD 2171 was recently evaluated in a phase I clinical trial in patients with advanced solid tumors.[59]

Vandetanib (Zactima®, ZD 6474) is an orally available inhibitor of VEGFR-2 and EGFR tyrosine kinase activity. In preclinical studies, vandetanib blocked *in vivo* phosphorylation of VEGFR and EGFR, and prevented the growth of transplanted human xenografts in nude mice.[60] However, a phase II trial of vandetanib in patients with previously treated metastatic breast cancer has yielded disappointing results.[61] Forty-six patients were enrolled, and the primary endpoint of objective response was not met (there were no objective responses reported). Diarrhea and rash were reported by 26% of patients; seven patients in the 300 mg cohort had asymptomatic prolongation of the QTc interval. These results indicate that vandetanib monotherapy is generally well tolerated, but has limited efficacy in patients with refractory metastatic breast cancer.

Vatalanib (PTK 787, ZK 222584) is an oral angiogenesis inhibitor that targets all known VEGFRs, including VEGFR-1, -2, and -3, PDGFR, and KIT. The feasibility and safety of PTK 787 in patients with advanced colorectal cancer was demonstrated in a recent phase I study.[62] Expansion of vatalanib in other indications, including AMD, has yet to be explored.

Pazopanib (GW 786034) is a TKI that targets VEGFR-1, -2, and -3, PDGFR, and KIT. A phase I study demonstrated activity in various types of advanced solid tumors.[63] In a phase II trial, pazopanib treatment resulted in stable disease or partial response in 42% (25/60) of patients at 12 weeks.[64] Adverse events included hypertension, fatigue, diarrhea, nausea, and proteinuria. Surprisingly, no cases of hand-and-foot syndrome were reported and only one case of bleeding occurred. Results appear encouraging and phase II/III trials are underway. A placebo-controlled phase III trial is ongoing in patients with untreated or cytokine-treated renal-cell carcinoma.[65]

Tivozanib (AV-951, KRN 951) is an oral TKI specific for VEGFR-1, -2, and -3. Tivozanib potently inhibits VEGF-induced VEGFR-2 phosphorylation in endothelial cells and blocks VEGF-dependent, but not VEGF-independent, activation of MAPKs and subsequent proliferation.[66] Following oral administration to rats, tivozanib decreased microvessel density within tumor xenografts and decreased VEGFR-2 phosphorylation within tumor endothelium.[66] Tivozanib also inhibited tumor growth in a wide variety of human tumor xenograft

models, including lung, breast, colon, ovarian, pancreas, and prostate.[66] A phase I clinical trial of tivozanib involving 40 patients with advanced solid tumors has shown promising results. Notably, of the nine patients in the trial with renal-cell carcinoma, all achieved either a partial response or stable disease, and one patient exhibited a response lasting >30 months.[67] Phase II trials of tivozanib are currently being conducted.

Motesanib (AMG706) is an orally bioavailable inhibitor of VEGFR-1, -2, and -3, PDGFR, and KIT in preclinical models. The drug inhibits human endothelial cell proliferation induced by VEGF, but not by bFGF *in vitro*, and inhibits VEGF-induced vascular permeability in mice.[68] Oral administration of motesanib potently inhibited VEGF-induced angiogenesis in a rat corneal model and induced regression of established A431 xenografts.[68] In a phase I trial enrolling 71 patients with advanced refractory solid tumors, the most frequent adverse events were fatigue, diarrhea, nausea, and hypertension.[69,70] Thirty four (61%) patients had stable disease (at least through 1 month). Motesanib was well tolerated and there was evidence of antitumor activity. Additional studies of motesanib as monotherapy and in combination with various other agents are ongoing.

8.2 Post-Transcriptional Control

PTC 299 is a novel drug that acts to modulate VEGF at the post-transcriptional level by modifying the 5′ and 3′ untranslated regions of VEGF mRNA. Preclinical data has shown that PTC 299 inhibits the production of all isoforms of VEGF and blocks VEGF synthesis in a variety of tumor cell types, including breast, cervical, colorectal, gastric, lung, ovarian, pancreatic, prostate, and renal cancer cells.[23] In animal models, PTC 299 monotherapy reduced the concentrations of VEGF in tumors and plasma, reduced tumor blood vessel density, and inhibited tumor growth.[23] In a phase I study enrolling 52 subjects, interim analysis showed mild adverse events, including headache, dizziness, nausea, vomiting, and stomach discomfort.[25] No bleeding, clotting, hypertension, or proteinuria occurred. Thus, early clinical results indicate that PTC 299 is a promising therapeutic agent, with fewer adverse events than other anti-VEGF therapies.

9. Issues with VEGF Inhibitors

Although VEGF inhibitors represent the culmination of decades of research in the treatment of several disease states, a number of issues need to be addressed before their true benefit can be realized. It is difficult to measure the efficacy of VEGF inhibitors. In cancer, for example, although tumor regression has occurred in some cases, angiogenesis inhibitors are not typically cytotoxic; rather they will more often result in growth stasis. Thus, some of the current criteria used to define whether anti-VEGF therapies are efficacious may need to be modified.

Monoclonal antibodies have historically been considered the 'magic bullet' for therapeutic targeting of cytokines. However, there have been reports of endogenous antibodies that target these therapeutic mAbs, rendering them inactive.[71] One must therefore expect that these types of reactions will occur with anti-VEGF mAbs as well. In addition, pharmacoeconomic analysis is not advanced enough to justify the use of these expensive therapies.

Agents that block VEGF or VEGFRs may very well block or potentiate the effects of other ligands as well. It is difficult to determine what the long-term effects of blocking VEGF and its receptors may be. In clinical trials, a frequent adverse event observed with most VEGF inhibitors is a dramatic increase in the rate of thromboembolic events.[72] Additional studies are needed to inform the determination by practitioners of which patient populations are at risk for an adverse event so as to tailor therapy accordingly.

Common adverse effects of pegaptanib or ranibizumab injections include changes in vision or difficulties seeing, inflammation of different parts of the eye, increased pressure inside the eye, and increased sensitivity to light.[27] Ranibizumab may raise the risk of stroke in elderly people, especially if they have already had a stroke. In addition, many adverse effects may be caused by the actual injection procedure, rather than the drug itself, For example, the injections have been shown to carry a risk of infection.[27]

10. Beyond VEGF-Targeted Therapies

VEGF inhibitors are a milestone in drug development. Despite this, several issues (as mentioned above) make it unlikely that they will be useful in all patients. Again using the example of cancer, VEGF inhibitors appear to be valuable in many types of cancer, but not in all types, and trials using VEGF inhibitors either alone or in combination with chemotherapy have produced mixed results. Thus, it will be helpful to have diagnostic testing available to determine which patients would benefit from therapy. Ideally, patient populations would be identified that could benefit most by targeting a specific angiogenic growth factor or by treatment with a specific class of drug. More data are also needed on potential antagonism/synergy between certain agents in order to predict the most efficacious combinations, thereby enabling practitioners to overcome redundancies that are built into the angiogenic process. Emerging therapies that target different points in the angiogenic process

Table I. Current and investigational anti-vascular endothelial growth factor targets for age-related macular degeneration

Compound	Status
Pegaptanib (Macugen®)	US FDA approved
Ranibizumab (Lucentis®)	US FDA approved
Bevacizumab (Avastin®)	US FDA approved
Aflibercept (VEGF Trap)	Phase III
Sunitinib (Sutent®)	US FDA approved
Sorafenib (Nexavar®)	US FDA approved
Vatalanib (PTK 787, ZK 222584)	Phase II (discontinued)
Pazopanib (GW 786034)	Phase II
Motesanib (AMG 706)	Phase III

may potentially have fewer adverse effects and benefit certain patient populations that cannot be treated with anti-VEGF therapies. Table I lists ongoing trials of agents that target different mechanisms and regulators of angiogenesis.

10.1 Alternative Therapies in AMD

Anecortave acetate (Retaane®) is an angiostatic cortisene that has been shown to be effective in the treatment of AMD.[73] In an uncontrolled clinical series of 19 patients (8 male, 11 female; average age, 78.8 years) with standardized documentation of VA, anecortave acetate 15 mg administered as a posterior juxtascleral depot injection was safe and well tolerated, based on near acuity, need for magnification, and fluorescein angiography.[73] The study concluded that in eyes with occult CNV without recent progression or with residual neovascular activity after PDT, anecortave acetate may be an alternative therapeutic option before considering intravitreal anti-VEGF agents due to its less invasive character and lower risk profile.

Several natural supplements or compounds derived from natural sources have been investigated in experimental models of CNV. Astaxanthin (AST), for example, is a carotenoid found in marine animals and vegetables that has been investigated for its effects on the development of experimental CNV in mice.[74] In this study, mice with laser photocoagulation-induced CNV who were treated with AST exhibited a significantly lower CNV volume as compared to vehicle-treated animals, suggesting that AST supplementation might be a viable therapeutic strategy for suppressing AMD-associated CNV.[74]

10.2 Radiotherapy in AMD

Radiotherapy represents a promising adjunct to anti-angiogenesis therapies for the control of CNV in AMD. However, even though modern delivery systems permit relatively low dosages, there are risks of radiotherapy to ocular tissue, and its role remains questionable in light of advances in pharmacotherapy.[75]

11. Conclusions

Treatment of AMD prior to 2000 was limited to focal laser photocoagulation, a destructive procedure that produced a permanent scar in an effort to limit the spread of CNV. This procedure turned out to be viable only for treating extra-foveal CNV, and even then, it was not entirely effective. PDT with verteporfin emerged in 2000 as the first treatment proven to reduce the risk of vision loss in sub-foveal CNV. However, its efficacy was limited to classic or small CNV, and even though it is a relatively nondestructive form of therapy, it failed to improve vision in patients with AMD in clinical trials.

AMD typically manifests as the loss of central vision; as such, it represents a major threat to quality of life. In addition, in a recent review of available data on the economic impact of macular degeneration in the developed world, which included reports of direct and indirect medical costs as well as estimates of non-healthcare costs, there were substantial differences in caregiver support with increased AMD severity. Thus, the development and testing of therapeutic agents that prevent or delay the progression of AMD is urgently needed, from the standpoint of patient care and quality of life, as well as cost savings.[76]

VEGF plays an important role in promoting angiogenesis, vascular leakage, CNV infiltration, and fluid accumulation in neovascular AMD. Therefore, inhibition of VEGF holds the promise of more effectively preventing or delaying the progression of neovascular AMD. Pegaptanib was approved by the FDA in 2004 and ranibizumab in 2006 after extensive preclinical and clinical testing. Off-label usage of bevacizumab has also become fairly standard. VA gains associated with ranibizumab have proven to be particularly exciting, and ranibizumab has become the current gold standard for AMD therapy. However, as with many new therapies, there are unresolved issues with anti-VEGF-based therapies, including safety, cost, and dosing frequency.

Additional preclinical and clinical studies are needed to assess the effects of inhibition of VEGF at various levels in AMD and beyond. Clinical trials assessing combination therapies, in particular, pegaptanib with ranibizumab and bevacizumab, as well as verteporfin PDT in various combinations with these drugs, are needed. In addition, studies are needed to assess adverse events outside those proposed in current trials,

determine optimal dosing regimens and the benefits of retreatment after initial treatment, and to review cost effectiveness in more detail. Finally, the relationship between duration of vision loss and quality of life and/or functional impact of vision loss, and behavioral studies of those genetically at risk for AMD are as-yet relatively unexplored areas of research in the field of AMD.[46]

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Europäisches Patentamt

80298 München

Munich, 7 September 2016

Application No.: EP 12 700 590.8
Applicant: Regeneron Pharmaceuticals, Inc.

Our ref.: 9281-TPO / RN

Observations pursuant to Article 115 EPC regarding European patent application 12 700 590.8

In accordance with Article 115 EPC, Third Party Observations against European patent application EP 12 700 590.8 (EP 2 663 325 A1) are filed on behalf of

bioeq GmbH
Tölzer Straße 12
83607 Holzkirchen
Germany

For the reasons set forth below, the presently pending claims of said application are **not in compliance with the requirements of the EPC**.

RN:LA

I. Prior art

The following documents disclosing the subject-matter of the pending claims as filed on 17 December 2014 are provided:

Annex 1	Press Release of Regeneron dated 22 November 2010
Annex 2	Press Release of Regeneron dated 20 December 2010
Annex 3	Article in Retinal Physician (March 2010)

All documents were published before the earliest priority date of 13 January 2011 and are therefore prior art according to Article 54(2) EPC.

II. The European patent application EP 2 663 325 A1

1. Bibliographical data

Earliest priority date:	13 January 2011
Filing date:	11 January 2012
Latest expiry date (if granted):	11 January 2032
Designated contracting states:	AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR
Applicant:	Regeneron Pharmaceuticals, Inc.
Current state:	Examination is in progress

2. Status

The European patent application is currently undergoing examination.

The first office action of the Examining Division according to Article 94(3) EPC was issued on 21 August 2014 and raised objections under Article 84 and 83 EPC (lack of clarity and sufficiency of disclosure) and Article 56 EPC (lack of inventive step).

Applicant filed a reply including amended claims on 17 December 2014.

3. Claims

Pending claim 1 of EP 2 663 325 A1 filed with the reply on 17 December 2014 is directed to:

> *"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 two 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 4 weeks after the immediately preceding dose;*
> *wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1."*

Pending claims 2 to 6 specify the angiogenic eye disorder as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, and corneal neovascularization, respectively.

Pending claim 7 specifies the VEGF antagonist to comprise (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.

Pending claims 8 to 10 specify the route of administration as topical or intraocular administration, intraocular administration, or intravitreal administration, respectively.

Pending claims 11 and 12 specify that all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist, and 0.5 mg or 2 mg of the VEGF antagonist, respectively.

It is noted that a press article of Regeneron published on 28 September 2008 was cited by the Examining Division (ED) in its communication dated 21 August 2014 as document D13. This document relates to the results of the phase II study preceding VIEW-1 and VIEW-2 studies and mentions the VIEW studies and dosage regimens to be administered therein. However, according to the ED, since no results of the phase III study are presented, the disclosure is not enabled. The ED further noted that the results of the phase III study are presented in example 4 of EP 2 663 325.

However, this reasoning means that any document disclosing the results of the phase III clinical studies in which the claimed dosage regimen is used anticipates the subject-matter of pending claim 1.

The following discussion will show that at the earliest priority date the results of phase III clinical studies using the claimed dosage regimen showing a therapeutic effect had already been published.

3. Lack of novelty (Article 54 EPC)

3.1 Press release of Regeneron dated 22 November 2010 (Annex 1)

Regeneron published a press release summarising the results of the VIEW-1 and VIEW-2 studies on 22 November 2010, i.e. before the priority date.

Annex 1 discloses that VEGF Trap-Eye was administered every two months after three monthly loading doses (second page, third paragraph):

> *"In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5mg monthly, 2mg monthly, or 2mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5mg every month during the first year of the studies."* (emphasis added)

In this context, the 2 mg aflibercept dose administered in the first visit corresponds to the single initial dose of the claimed VEGF antagonist, the 2 mg aflibercept doses administered at weeks 4 and 8 correspond to two secondary doses of the claimed VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose, and the 2 mg aflibercept doses administered thereafter every 8 weeks correspond to the tertiary doses of the claimed VEGF antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline).

VEGF Trap-Eye is aflibercept ophthalmic solution (see first page, first paragraph of Annex I). According to paragraph [0007] of WO 2012/097019 A1

aflibercept is the same molecule as VEGFR1R2-FcΔC1(a) to which claim 1 refers.

According to Annex 1 the results of the VIEW studies show that *"all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month."* (cf. first page, first paragraph; emphasis added). This shows that a therapeutic effect is indeed obtained by treatment with a dosage regimen as required by the pending claims.

Further, Table 1 presented in Example 4 of EP 2 663 325 A1 is already shown on page 2 of Annex 1.

Thus, Annex 1 discloses all features of pending claims 1, 2 and 7 to 12.

3.2 Press release of Regeneron dated 20 December 2010 (Annex 2)

Regeneron published a further press release relating to the results of the studies COPERNICUS and DA VINCI on 20 December 2010, i.e. before the earliest priority date.

DA VINCI is a phase II study in patients with diabetic macular edema. In this study participants were randomized into one of five groups: one group receiving laser treatment (control group), two groups receiving 0.5 or 2 mg of VEGF Trap-Eye monthly, and two groups receiving three initial monthly doses of 2 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing (corresponding to the regimen defined in pending claim 1) or as-needed dosing (first page, penultimate paragraph).

Annex 2 reports that *"the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the [DA VINCI] study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month."* (cf. first page, penultimate paragraph; emphasis added).

Furthermore, Table 2 presented in Example 5 of EP 2 663 325 A1 is already shown on page 2 of Annex 2.

Thus, Annex 2 discloses all features of pending claims 1, 4 and 7 to 12.

3.3 Article in Retinal Physician (March 2010) (Annex 3)

A brief news article relating to the DA VINCI study and interim results thereof was published in the March 2010 issue of Retinal Physician and is available on the homepage (http://www.retinalphysician.com/printarticle.aspx?articleID=104007).

Annex 3 discloses the dosing groups in the last paragraph of the article "VEGF Trap Has Positive DME Data" (on page 2/4), including two groups receiving three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline, weeks 4 and 8), followed through 24 weeks by either dosing every 8 weeks (corresponding to the regimen defined in pending claim 1) or as-needed dosing.

Annex 3 further describes that the DA VINCI study showed positive interim results (first paragraph of the article) and that each one of the dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean

improvements in visual acuity compared to patients receiving laser therapy (penultimate paragraph of the article).

Thus, Annex 3 also discloses all features of pending claims 1, 4 and 7 to 12.

III. Conclusion

Results from phase III clinical studies showing the successful use of the dosage regimen of pending claim 1 were published before the priority date of EP 2 663 325 A1. The subject-matter of pending claim 1 is therefore not novel.

The same is true for the subject-matter of pending claims 2, 4 and 7 to 12.

Pending claims 3, 5 and 6 relating to different angiogenic eye disorders are considered to be obvious in view of the results of the cited studies.

Thus, in view of the published results all pending claims do not meet the requirements of the EPC.

Maiwald Patentanwalts GmbH
(Andrea Lasar)

Encls.
Annex 1-3

ANNEX 3

Article Date: 3/1/2010

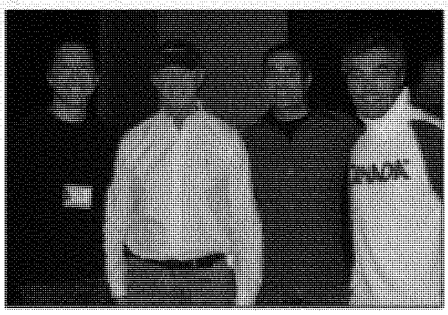
SUBSPECIALTY NEWS

Fellows Forum Marks 10th Year

Dr. Steve Charles is Guest Lecturer.

■ The tenth annual Retina Fellows' Forum took place on Jan. 29 and 30 at the Westin River North in frigid Chicago. Eighty North American fellows participated in an educational and social program that has become a much-anticipated fixture of the final year of vitreoretinal training.

As in past years, the fellows spent considerable time in the lecture hall with a panel of volunteer faculty, led by Course Director David Chow, MD, and co-directors Carl Awh, MD, and Tarek Hassan, MD. Ophthalmologists Dean Eliott, Phil Ferrone, Jeff Heier, Nancy Holekamp and Peter Kaiser completed the faculty.



From left, Drs. Carl Awh, Steve Charles (Distinguished Guest Lecturer), Tarek Hassan and David Chow.

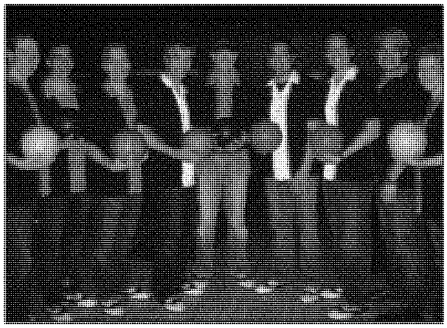
The meeting began on Friday evening with an AMD Symposium and sessions on Diagnostic Instrumentation and Pediatric Retina. New to the meeting were the inaugural "Faculty Debates," in which the faculty debated the following topics: Avastin vs. Lucentis; Pneumatic Retinopexy vs. Scleral Buckle vs. Vitrectomy, and Fluorescein Angiography vs. OCT. Topics were assigned to the faculty, who relied upon clinical data, personal experience, and (most effectively) humor to defend their positions.

A Friday evening reception and dinner provided the first opportunity for the "graduating class" of 2010 fellows to socialize with their peers, the faculty, and representatives from industry.

Saturday offered a full day of panel-driven discussions on Diabetic Retinopathy, Retinal Vascular Occlusion, Medical and Surgical "Pearls," "News You Can Use," and advice on career and lifestyle management. As always, a highlight of the meeting was the Distinguished Guest Lecture, this year delivered by Steve Charles, MD. Dr. Charles captivated and inspired the audience with his talk on "Technology, Technique, and the Pursuit of Happiness."

For the 10th consecutive year, Bausch & Lomb provided essential support as the major sponsor of the Retina Fellows' Forum. Genentech provided a generous educational grant to support the opening AMD symposium. Thirteen additional companies representing a cross-section of devices and services important to vitreoretinal practice provided financial support and presented updates to the group about their businesses.

The prestigious and competitive Bausch & Lomb Retina Fellows' Forum Research award went to Arghavan Almony, MD, of the Barnes Retina Institute for her paper, "Small-Gauge Vitrectomy Does Not Protect Against Nuclear Sclerotic Cataract." Dr. Almony will present her paper at the 2010 Annual Meeting of the American Society of Retina Specialists as a specially recognized lecture.



The Fellows Forum faculty, from left, Drs. Phil Ferrone, Jeff Heier, Dean Eliott, David Chow, Steve Charles, Tarek Hassan, Carl Awh, Peter Kaiser, and Nancy Holekamp.

The meeting concluded with dinner, an informal awards ceremony, and the 5th Annual Retinal Fellows' Forum Bowling Tournament. Fellows and corporate representatives were divided into teams captained by the faculty. Phil Ferrone's team emerged victorious, aided in no small measure by his score of 220, the highest of the evening.

The 11th Annual Retina Fellows Forum will be held in Chicago on Friday, Jan. 28 through Saturday, Jan. 29, 2011.

In addition to Bausch & Lomb and Genentech, corporate support for the event was provided by Alcon, Alimera Sciences, Allergan, Carl Zeiss Meditec, Dutch Ophthalmic, Insight Instruments, Iridex, MedOne Surgical, Neovista, QLT, Quantel Medical, Synergetics and Volk Optical.

VEGF Trap Has Positive DME Data

Study Compared Drug to Laser.

■ Regeneron Pharmaceuticals and Bayer HealthCare AG reported that VEGF Trap-Eye showed positive interim results versus laser in a phase 2 study in patients with diabetic macular edema.

The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME — macular laser therapy — was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the one-year study.

"The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high levels of vascular endothelial growth factor are present," said Diana Do, MD, the principal investigator for the study and assistant professor of Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine in Baltimore.

Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared to patients receiving macular laser therapy (2.5 letters gained) at week 24. VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.

In this double-masked, prospective, randomized, multicenter phase 2 trial, entitled DA VINCI, 219 patients with clinically significant DME with central macular involvement were randomized to five groups. The control group received macular laser therapy at week one, and patients were eligible for repeat laser treatments, but no more frequently than at 16-week intervals. Two groups received monthly doses of 0.5 or 2.0 mg of VEGF Trap-Eye throughout the six-month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every eight-week dosing or as-needed dosing with specific repeat dosing criteria. Patients are continuing on the same dosing regimens for an additional 24 weeks.

Avastin Seen as Equal to Lucentis

But Genentech Takes Issue With Study.

BY JERRY HELZNER, SENIOR EDITOR

■ Researchers at Kaiser Permanante Southern California who treated 324 wet AMD patients with Avastin (bevacizumab) and 128 patients with the same disease with Lucentis (ranibizumab) found little difference between the two Genentech drugs after 12 months, both in terms of stabilizing visual acuity and in reported side effects.

Genentech was quick to point out factors that could have biased the data.

The researchers, who reported their results in the February issue of *Ophthalmology*, acknowledged the observational and nonrandomized nature of the study. However, lead author Donald Fong, MD, said that the study "should reassure patients and ophthalmologists that bevacizumab appears to be just as effective as ranibizumab."

Though the Permananente study was uncontrolled and the bevacizumab patients had an average age of 78, significantly younger than the ranibizumab patients, the researchers found that approximately one-quarter of all patients achieved close to 20/40 vision at 12 months, with little difference in adverse events.

The larger and more rigorous CATT study, which will compare Avastin and Lucentis on a head-to-head basis, is currently underway. Initial results are expected sometime in 2011.

Genentech took issue with some aspects of the Kaiser Permanente study. In a prepared statement, the company said:

"We are aware of the retrospective analysis published in the journal *Ophthalmology* titled 'Intravitreal Bevacizumab and Ranibizumab for Age-Related Macular Degeneration.' Genentech continues to believe Lucentis is the most appropriate medicine for people with wet age-related macular degeneration because it was specifically designed, formally studied, manufactured for intraocular delivery and is approved by FDA. At the same time, Genentech does not interfere with doctors' prescribing choices and believes that they should be able to prescribe the treatment they believe is most appropriate for their patients."

Genentech further asserted that "this was an uncontrolled and unmasked retrospective case analysis, with too few patients and too short a duration to adequately assess differences between the two treatment groups."

Genentech quoted Dr. Fong as stating in the article that "the sample size of the current study does not have sufficient power to determine whether there are any differences in safety." The author also notes in the conclusion of the paper, "Because the study is a nonrandomized comparison, selection bias could mask a true treatment difference."

According to Genentech, "The results beg the question as to why a higher percentage of patients switched off of Avastin than Lucentis (23% vs. 3% initially treated with Lucentis); however, the author offers only a limited explanation of this occurrence stating, 'the availability of ranibizumab most likely accounted for some of the changes observed in the bevacizumab group.'"

IN BRIEF

■ **VEGF Trap a future gold standard therapy?** In a survey of 91 US and European retina specialists, Regeneron/Bayer's as yet unapproved aflibercept (VEGF Trap-Eye) was named as a therapy for wet AMD that has the potential to reach gold-standard status. VEGF Trap-Eye is currently completing its pivotal phase 3 trials.

Decision Resources, a leading research and advisory firm for pharmaceutical and healthcare issues, reported that both Genentech's Lucentis and Regeneron/Bayer's VEGF Trap-Eye can be expected to earn Decision Resources' proprietary clinical gold standard status for wet AMD in 2013 and 2018.

A unique future gold standard cannot be identified because neither thought-leader opinion nor available clinical data can show that VEGF Trap-Eye has any advantages or disadvantages relative to Lucentis in terms of efficacy, safety and tolerability or delivery attributes.

However, Decision Resources believes that are still unmet medical needs in the treatment of wet AMD.

■ **Lux files for uveitis drug approval**. Lux Biosciences, Inc. has submitted regulatory filings to both the FDA and European Medicines Agency (EMA) seeking marketing approval for its investigational drug Luveniq (LX211) oral voclosporin for the treatment of noninfectious uveitis involving the intermediate or posterior segments of the eye.

Lux said efficacy of LX211 was demonstrated in two controlled, randomized, multicenter trials including data from 450 patients at 56 sites in seven countries. The safety data include a total of 2,110 subjects who received voclosporin during its clinical development in uveitis and psoriasis, about 500 of whom were treated for more than 36 weeks and about 200 for more than 52 weeks.

LX211 had previously received orphan drug status from the FDA and EMA, and fast-track status from the FDA. Based on the latter, Lux Biosciences has requested priority review from the FDA.

■ **Wnt pathway plays role in DR**. Scientists have identified a molecular pathway that appears to play a vital role in diabetic retinopathy. In a study appearing in the *American Journal of Pathology*, researchers show that retinal levels and nuclear translocation of beta-catenin, a key effector in the canonical Wnt pathway, were increased in humans with DR and in three DR models. Retinal levels of low-density lipoprotein receptor-related proteins 5 and 6, coreceptors of Wnts, were also elevated in the DR models.

The high glucose-induced activation of beta-catenin was attenuated by aminoguanidine, suggesting that oxidative stress is a direct cause for the Wnt pathway activation in diabetes. Indeed, Dickkopf homolog 1, a specific inhibitor of the Wnt pathway, ameliorated retinal inflammation, vascular leakage, and retinal neovascularization in the DR models. Dickkopf homolog 1 also blocked the generation of reactive oxygen species induced by high glucose, suggesting that Wnt signaling contributes to the oxidative stress in diabetes. This indicates that the Wnt pathway plays a pathogenic role in DR and represents a novel therapeutic target. **RP**

ERRATUM

In the article "Short-pulse Laser Treatment: Redefining Retinal Therapy," in the January/February 2010 issue of *Retinal Physician*, Figure 1 was mislabeled. The image is not of a rabbit eye, but of a human eye. *Retinal Physician* regrets the error.

Retinal Physician, Issue: March 2010

REGENERON
science to medicine®

December 20, 2010

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)

In Phase 3 study in CRVO, 56 percent of VEGF Trap-Eye patients gained at least 15 letters of vision compared to 12 percent in control group; VEGF Trap-Eye patients on average gained 17 letters of vision compared to mean loss of 4 letters in control group

In Phase 2 study in DME, patients in all VEGF Trap-Eye dose groups, including VEGF Trap-Eye dosed every two months, maintained or increased vision gains through 52-weeks

Regeneron to receive $20 million in milestone payments in connection with VEGF Trap-Eye program

Tarrytown, NY, USA, and Berlin, Germany, December 20, 2010 -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Bayer HealthCare today announced positive top-line results for VEGF Trap-Eye (aflibercept ophthalmic solution) in the COPERNICUS study, which is led by Regeneron, the first of two Phase 3 studies in patients with macular edema due to central retinal vein occlusion (CRVO). In this trial, 56.1 percent of patients receiving VEGF Trap-Eye 2 milligrams (mg) monthly gained at least 15 letters of vision from baseline, compared to 12.3 percent of patients receiving sham injections ($p<0.0001$), the primary endpoint of the study. Patients receiving VEGF Trap-Eye 2mg monthly gained, on average, 17.3 letters of vision compared to a mean loss of 4.0 letters with sham injections ($p<0.001$), a secondary endpoint. The second Phase 3 study, GALILEO, is currently ongoing and is led by Bayer HealthCare.

VEGF Trap-Eye was generally well tolerated and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. A total of 114 patients were randomized to receive VEGF Trap-Eye and 73 patients to the control arm. Serious ocular adverse events in the VEGF Trap-Eye group were uncommon (3.5%) and were more frequent in the control group (13.5%). The incidence of non-ocular serious adverse events was generally well-balanced between the treatment arms. There were no deaths among the 114 patients treated with VEGF Trap-Eye and two in the 73 (2.7%) patients treated with sham injections.

"In the COPERNICUS trial, patients treated with VEGF Trap-Eye experienced a marked improvement in vision," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "If these results are confirmed by data from the GALILEO study, expected in the second quarter of 2011, VEGF Trap-Eye could provide patients and physicians with a new treatment option for central retinal vein occlusion."

"After reporting positive results from our global Phase 3 program (VIEW 1 and VIEW 2 studies) for the treatment of the neovascular form of age related macular degeneration (wet AMD), we are pleased to also have a positive Phase 3 trial with VEGF Trap-Eye in central retinal vein occlusion, a potential second indication," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "We are working diligently with Regeneron to prepare regulatory filings for VEGF Trap-Eye in wet AMD to submit in the first half of 2011."

Detailed results for COPERNICUS will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

Regeneron will receive a $10 million milestone payment from Bayer HealthCare in connection with the COPERNICUS trial meeting its primary endpoint and received a $10 million milestone payment in December 2010 for the positive VIEW 1 and VIEW 2 trial results in wet AMD.

Phase 2 DME Results
Regeneron and Bayer HealthCare also reported 52 week follow-up results from the Phase 2 DA VINCI study in patients with diabetic macular edema (DME). In this study, the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month. Based on these positive results, Regeneron and Bayer HealthCare are discussing plans to initiate Phase 3 studies.

In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled **DA VINCI** (**D**ME **A**nd **V**EGF Trap-Eye: **IN**vestigation of **C**linical Impact), 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. Two groups

received monthly doses of 0.5 or 2mg of VEGF Trap-Eye throughout the 12-month dosing period. Two groups received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing or PRN (as-needed) dosing with very strict repeat dosing criteria. Mean gains in visual acuity versus baseline were as follows:

	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline[1] (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**

*Following 3 initial monthly doses
**p<0.01 versus laser
[1] Primary endpoint

No significant differences among the VEGF Trap-Eye arms were observed. Approximately 80 percent of the VEGF Trap-Eye patients and 75 percent of the laser patients remained in the study through 52 weeks.

VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study.* The most common adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent ocular adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, ocular redness (hyperemia), and increased intraocular pressure. The incidence of non-ocular serious adverse events was generally well balanced between all treatment arms. There were six deaths (3.4%) among the 175 patients treated with VEGF Trap-Eye and one (2.3%) in the 44 patients treated with laser over 12 months. Detailed results for DA VINCI will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

About the Phase 3 CRVO Program
Patients in the COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) and the identical GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) studies receive six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. Patients in the COPERNICUS trial were randomized in a 3:2 ratio with 114 patients randomized to receive VEGF Trap-Eye and 73 randomized to the control arm. At the end of the initial six months, all patients randomized to VEGF Trap-Eye are dosed on a PRN (as needed) basis for another six months. In the COPERNICUS trial, patients randomized to sham injections in the first six months are eligible to cross over to VEGF Trap-Eye PRN dosing in the second six months. During the second six months of the studies, all patients are eligible for rescue laser treatment. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity.

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

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

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

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

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO), and other eye diseases and disorders. In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval for the treatment of wet AMD in Europe and the U.S. in the first-half of 2011.

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

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

About Bayer HealthCare
The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

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

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

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*As noted during our investor teleconference on December 20, 2010, the press release inadvertently omitted certain information, which

Regeneron does not consider to be material. To reflect inclusion of such omitted information, this sentence would be replaced with the following: "In this study, VEGF Trap-Eye was generally well-tolerated and no patients experienced ocular drug-related serious adverse events. With respect to the number of patients with non-ocular serious adverse events judged by investigators to be drug-related, there were none during the first six months of the study and one in the second six months."

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REGENERON
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November 22, 2010

Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration

In both studies, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, achieved primary endpoint compared to ranibizumab dosed every month
Regulatory applications for marketing approval planned in first-half of 2011

TARRYTOWN, N.Y. and BERLIN, Nov. 22, 2010 /PRNewswire-FirstCall/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare today announced that in two parallel Phase 3 studies in patients with the neovascular form of age-related macular degeneration (wet AMD), all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab.

Further results will be presented at the Angiogenesis Conference in February 2011. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval in Europe and the U.S. in the first-half of 2011 based on the positive results of the VIEW 1 and VIEW 2 trials.

In the North American VIEW 1 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 95 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 95 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. In the international VIEW 2 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 96 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 96 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart.

"The currently available anti-VEGF therapies have significantly advanced the treatment of wet AMD, actually improving vision in many patients. However, monthly injections are required to optimize and maintain vision gain over the long-term," said Ursula Schmidt-Erfurth, M.D., Professor and Chair of the Department of Ophthalmology at the University Eye Hospital in Vienna, Austria and the VIEW 2 Principal Investigator. "The results of the VIEW studies indicate that VEGF Trap-Eye could establish a new treatment paradigm for the management of patients with wet AMD --- predictable every-other-month dosing without the need for intervening monitoring or dosing visits."

"In an effort to avoid the inconvenience of monthly office visits and the burden of monthly injections into the eye for their wet AMD patients, retinal specialists have tried to extend the benefits of the existing anti-VEGF therapy with less frequent dosing. A growing body of data suggests that this practice may result in inconsistent visual acuity outcomes," said Jeffrey Heier, M.D., a clinical ophthalmologist and retinal specialist at Ophthalmic Consultants of Boston, Assistant Professor of ophthalmology at Tufts School of Medicine, and Chair of the Steering Committee for the VIEW 1 trial. "A critical goal of these studies was to demonstrate that VEGF Trap-Eye could achieve robust improvements in vision and maintain them over time with a more convenient every-other-month dose. Achievement of this goal could be important for patients, care givers, and physicians."

In the VIEW 1 study, patients receiving VEGF Trap-Eye 2mg monthly achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly; patients receiving VEGF Trap-Eye 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 VEGF Trap-Eye in the VIEW 1 study and all dose groups in the VIEW 2 study were not statistically different from ranibizumab in this secondary endpoint.

A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation,

breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

In the second year of the studies, patients in VIEW 1 and VIEW 2 will continue to be treated with the same dose per injection as in the first year but administered only every three months, or more often for any worsening of AMD, based on protocol-defined criteria (called "quarterly capped PRN" dosing).

About the VIEW Program

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

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

The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain visual acuity at the end of one year, compared to ranibizumab patients. Visual acuity is measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.

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

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

*Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart
**Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)
*** Test for superiority
NS=non-significant

About Wet AMD

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

About VEGF Trap-Eye

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

VEGF Trap-Eye is also in Phase 3 development for the treatment of Central Retinal Vein Occlusion (CRVO), another major cause of blindness, in two identical studies. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron and the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. Initial data from the CRVO program are anticipated in early 2011.

VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). In February 2010, Regeneron and Bayer HealthCare announced that treatment with VEGF Trap-Eye in the Phase 2 DA VINCI (DME And VEGF Trap-Eye: INvestigation of Clinical Impact) study demonstrated a statistically significant improvement in visual acuity versus baseline after six months of treatment compared to focal laser therapy, the primary endpoint of the study. Initial one-year results from this trial will be available before the end of this year.

About Regeneron Pharmaceuticals

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

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward Looking Statement

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

Bayer Forward-Looking Statements

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

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SOURCE Regeneron Pharmaceuticals, Inc.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	9281-TPO/RN

	Description of document	Original file name	Assigned file name
1	Non-patent literature filed by a third party	Annex 1 (Regeneron VIEW results).PDF	TDOCNPL-1.PDF
2	Non-patent literature filed by a third party	Annex 2 (Regeneron DA VINCI results).PDF	TDOCNPL-2.PDF
3	Non-patent literature filed by a third party	Annex 3 (Retinal Physician DA VINCI results).PDF	TDOCNPL-3.PDF
4	Observations by third parties (Art. 115 EPC)	TPO.pdf	TIPA1-1.pdf

Signatures

Place:	**Munich**
Date:	**07 September 2016**
Signed by:	**Andrea Lasar 13617**
Representative name:	**Andrea Lasar**
Capacity:	**(Representative)**

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	4624725
Application number	EP12700590.8
Date of receipt	07 September 2016
Receiving Office	European Patent Office, The Hague
Your reference	9281-TPO/RN
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (1 p.) TDOCNPL-2.PDF\Annex 2 (Regeneron DA VINCI results).PDF (4 p.) TIPA1-1.pdf\TPO.pdf (8 p.) ep-sfd-request.xml TDOCNPL-1.PDF\Annex 1 (Regeneron VIEW results).PDF (4 p.) TDOCNPL-3.PDF\Annex 3 (Retinal Physician DA VINCI results).PDF (4 p.)
Submitted by	CN=Andrea Lasar 13617
Method of submission	Online
Date and time receipt generated	07 September 2016, 15:38 (CEST)
Message Digest	A0:C5:92:58:0A:A1:B8:B1:B0:5E:E0:60:C2:8A:D5:74:03:26:0F:22

Correction by the EPO of errors in debit instructions filed by eOLF

Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

Europäisches Patentamt
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Contact Customer Services at www.epo.org/contact

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Date
13.09.2016

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Communication pursuant to Rule 114(2) EPC

Please find enclosed observations by a third party concerning the patentability of the invention of the above-mentioned patent application. That person is not a party to the proceedings before the EPO (Art. 115 EPC).

Under Rule 114(2) EPC you may comment on the observations.

For the Examining Division

European Patent Office
Bob-van-Benthem-Platz 1
80469 Munich

Anonymous third party observation regarding EP 12700590.8

This is a Third Party Observation pursuant to Article 115 EPC in respect of pending European Patent Application EP12700590.8/2663325 (hereinafter "application") filed on 11 January 2012 in the name of Regeneron Pharmaceuticals, Inc.

The subject matter of the set of claims as filed on 17 December 2014 and currently pending in the application is not patentable under the terms of Articles 52-57 EPC.
Furthermore, the claimed subject matter is not disclosed in the application in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

I. Pertinent Documents

In the following it is referred to document *D13* cited as such in the Examination Procedure, as well as documents *OBS1-OBS8*, which are considered highly relevant with regard to patentability

of the claimed subject matter, all of which represent prior art according to Article 54(2) EPC.

D13: XP002674126

OBS1: Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008

OBS2: Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008

OBS3: Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007

OBS4: WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119

OBS5: Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8

OBS6: Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009

OBS7: Mousa and Mousa, Biodrugs 2010; 24(3); 183-194

OBS8: Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

II. Claims pending in the application

Claim 1 is the sole independent claim currently pending in the application and relates to:

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 **[feature a]**
followed by
- two or more secondary doses of the VEGF antagonist **[feature b]**,
followed by
- one or more tertiary doses of the VEGF antagonist **[feature c]**;
wherein
- each secondary dose is administered 4 weeks after the immediately preceding dose **[feature b1]**;
wherein
- each tertiary dose is administered 8 weeks after the immediately preceding dose **[feature c1]**;
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 **[feature d]**;
and wherein
- the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1 **[feature e]**.

The remaining dependent claims will be referred to in the respective passages below, if applicable.

III. Novelty of the Subject Matter of Claims 1-12

The subject matter of independent claim 1 is not novel over documents *D13*, *OBS1* and *OBS2*.

Independent claim 1 is a second medical use claim, which use is in a treatment of particular angiogenic eye disorders **[feature d]**, characterized by a particular dosage regimen **[features a - c]** of a specific VEGF antagonist **[feature e]**.

The exact same dosage regimen was used in Regeneron's phase 3 trial "VIEW 2" and in this context was available to the public long before the earliest priority date of 13 January 2011.
Evidence for the public availability of the critical details of the VIEW 2 study is provided by prior art documents *D13*, *OBS1* and *OBS2*:

D13, also cited by the Examining Division in the Examination Procedure, describes at page 2 third paragraph, that Regeneron's phase 3 trial aims *inter alia* at "evaluating VEGF TRAP-Eye dosed [...] 2 mg every 8 weeks (following 3 monthly doses)". Such a dosage regimen is covered by claim 1 as it comes down to administering the VEGF antagonist at week 0 **[feature a]**, week 4 and 8 **[feature b1]** and week 16 **[feature c1]**.

Similarly, this dosage regimen was also presented at the 2008 Retina Society Meeting as can be seen from the table at page 29 of *OBS1*, which shows a dosage regimen (row labeled "2.0 mg q8 wks") falling within the definition of that recited in claim 1.

A dosage regimen as claimed is furthermore foreseen in the "Descriptive Information" of this VIEW 2 Clinical Trial, available online in its version of 17 March 2008 (see the third Intervention "Arm 3" at page 2 of *OBS2*).

While in the above cited documents (*D13*, *OBS1*, *OBS2*) the tested compound is denominated "VEGF TRAP-Eye", this designation was known at the priority date of the application for a person skilled in the art as a synonym for "aflibercept" which is encoded by SEQ ID NO:1. Importantly, structural information concerning VEGF TRAP-Eye/aflibercept was at the disposal of the person skilled in the art since 2006, as is apparent from documents *OBS3-OBS8* as follows:

OBS3 is a quality report published on 7 November 2007 by the applicant Regeneron. Such a quality report as required by the US Security and Exchange Commision is immediately available on the internet.

In particular at page 15 and 17 of *OBS3* "VEGF TRAP" is identified as "aflibercept" and at page 19 it is stated that "VEGF TRAP-Eye is a form of the VEGF TRAP [...] suitable for direct injection into the eye". Comparable information is also contained in *OBS8.* From here it is clearly apparent that VEGF TRAP-Eye is aflibercept.
The fact that these two terms are synonym is also acknowledged by the Examining Division (see e.g. item 5 of the Communication dated 21 August 2014).

Knowing that the compound tested in the VIEW 2 trial publicized by *D13* and *OBS1-OBS2* is aflibercept, the person skilled in the art also was in a position to obtain the relevant structural information as such information was available, e.g. from:

OBS4, which is a 2006 report of the WHO that discloses on pages 118 and 119 the chemical structure, i.e. the amino acid sequence of aflibercept, which
- comprises the three elements aa 27-129, aa 130-231 and aa 232-457 of SEQ ID NO:2 of the present application that are characteristic for VEGFR1R2-FcΔC1(a) (as specified in par. [0023] of the specification of the present application), and
- is encoded by SEQ ID NO:1 of the present application **[feature e]**.

Of note, this peptide sequence of aflibercept is identical with the sequence of the particular VEGF antagonist of claim 7 having an amino acid sequence defined by residues 27 to 457 of SEQ ID NO:2 of the application.

Additionally, also documents *OBS5-OBS7* represent the knowledge of a person skilled in the art with respect to the structure of VEGF TRAP-Eye/aflibercept, namely:

OBS5 states at page 3, left column, third paragraph that "VEGF TRAP-Eye and aflibercept" (the oncology product) have the same molecular structure" and this reference also discusses the VIEW 2 study, namely its "bimonthly" **[feature c1]** dosage regimen (see page 4, right column, second paragraph and page 5, right column, first paragraph).

Similarly, *OBS6* states at page 1559, right column, that "aflibercept [is] also known as a VEGF Trap-Eye" and further outlines the structure of this fusion protein. Interestingly, this review focuses on treatment of diabetic retinopathy hence underlining the comparable requirements for the treatment of the different angiogenic diseases **[feature d]** recited in the pending claims.

Finally, *OBS7* repeats the identity of aflibercept and VEGF Trap-Eye and also points to the VIEW 2 study (see page 187).

From the foregoing, it is apparent that there can be no doubt that the person skilled in the art at the earliest priority date was aware that the compound to be tested in the VIEW 2 trial, which trial used the claimed dosage regimen, is aflibercept and its detailed structure being known since 2006.

In light of the above, the subject matter of claims 1 and 7 can by no means be regarded as novel.

As the subject matter of claims 2-6 consists in a mere subdivision of the different diseases listed in claim 1 **[feature d]**, the ascertained lack of novelty likewise applies to the subject matter of these claims.

Claims 8-10 specify administration routes, namely claim 8 pertains to "topical" or "intraocular" administration (the latter being also the subject matter of claim 9), and claim 10 further specifies "intraocular" as being "intravitreal".
While "intraocular" injection of VEGF Trap-Eye is e.g. disclosed at pages 18 and 19 of *OBS3*, the more specific "intravitreal" administration corresponds to the administration route used in the VIEW 2 trial as it is e.g. apparent from the Official title of the study (see *OBS2*): "A Randomized, Double Masked, Active Controlled, Phase 3 study of the Efficacy, Safety and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)" and the Conclusion section on page 28 of *OBS1*.
The features of claims 8-10 are thus not novel as well.

Claim 11 further specifies with respect to claim 1 that "all doses comprise from about 0.5 mg to about 2 mg" of the VEGF antagonist and claim 12 is restricted to the respective end points with claim 12(a) reciting "0.5 mg" and claim 12(b) reciting "2 mg".
These particular doses are anticipated by the VIEW 2 clinical trial (see *D13*; *OBS1* page 29; and *OBS2*) and thus lacks novelty

Claim 12(a) and (b) further specify that "all doses of the VEGF antagonist comprise 0.5 mg/2 mg of the VEGF antagonist", respectively. The use of constant amounts of aflibercept/VEGF Trap-Eye in the VIEW 2 trial is known from page 29 of *OBS1*.
The features of claim 11 and 12 are thus not novel.

The subject matter of claims 1-12 currently pending in the application thus contravenes Article 54 EPC.

IV. Inventive Step and Sufficiency of Disclosure of the Subject Matter of Claims 8-11 and 12

The alternative potential administration route recited in claim 8 that is not known from *OBS*1-3, i.e. "topical administration" which according to paragraph [0028] of the application is an administration "via eye drops or other liquids, gels, ointment or fluid", though certainly desirable as it would overcome the disadvantages associated with intravitreal injections such as being invasive and thus requiring a skilled specialist. However as this administration route is not supported by any data in the application it is hence to be regarded as an obvious alternative to the intraocular administration that is readily available to a person skilled in the art, i.e. lacks an inventive step.
Even more, the absence of experimental evidence gives rise to the conclusion that topical administration does not provide a solution to the technical problem of treating angiogenic eye disorder with a VEGF antagonist.

Similarly, regarding lower doses of 0.5 mg (claim 12(a)) or between 0.5 and 2 mg (claim 11) it has to be noted that these doses do not appear to contribute to an inventive step of the claimed second medical use.
This because, first, the exact value of 0.5 mg corresponds to the amount also used in the "VIEW 2" and previous Regeneron trials in connection with a monthly dosage regimen and further it is the effective concentration at which Ranibizumab is used in these studies for comparison (see *D13*, *OBS1* and *OBS2*). Therefore the choice of this minimal dose seems to be an obvious one for the person skilled in the art.
Second, the application does not even provide any data of the combination of "0.5 mg" and "bimonthly dosing" **[feature c1]**, so that it is questionable whether this dosage regimen solves the technical problem of providing an improved treatment of angiogenic eye disorders with a VEGF antagonist, at all.

The remarks above with regard to the lack of an inventive step for the subject matter of claims 11 and 12(a), namely that there are no supporting data on file demonstrating the effect of these administration regimens also give rise to a lack of sufficiency of disclosure.

The set of claims currently pending in the application thus also contravenes Articles 56 and/or 83 EPC.

In conclusion, the set of claims pending in European Patent Application EP12700590.8/2663325 does not fulfill the requirements of the EPC and should thus not be allowed by the Examining Division.

Encl: *OBS1-OBS8*

OBS 2

View of NCT00637377 on 2008_03_17

ClinicalTrials Identifier: NCT00637377
Updated: 2008_03_17

Descriptive Information

Brief title	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2).
Official title	A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD).

Brief summary

This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Active Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (ie, prevention of moderate vision loss) Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52 Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: The proportion of subjects who gain at least 15 letters of vision at Week 52 Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in total NEI VFQ-25 score at Week 52

	Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in CNV area at Week 52 Time Frame: week 52 Safety Issue? Yes
Enrollment	1200 (Anticipated)
Condition	Macular Degeneration
Arm/Group	Arm Label: Arm 3 Experimental n/a
Arm/Group	Arm Label: Arm 1 Experimental n/a
Arm/Group	Arm Label: Arm 2 Experimental n/a
Arm/Group	Arm Label: Arm 4 Active Comparator n/a
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 1 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 2 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye Arm Label: Arm 3 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: Ranibizumab Arm Label: Arm 4 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
URL	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
URL	http://www.fda.gov/medwatch/safety.htm
URL	http://www.clinicalstudyresults.org
See also	Click here and search for drug information provided by the FDA
See also	Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product
See also	

Click here to find results for studies related to marketed products

Recruitment Information

Status Not yet recruiting
Start date 2008-03
Last follow-up date 2011-09 (Anticipated)
Criteria

Inclusion Criteria:
1. Signed informed consent.
2. Men and women ≥ 50 years of age.
3. Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
4. ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye at 4 meters.
5. Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria:
1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
3. Any prior treatment with anti-VEGF agents in the study eye.
4. Total lesion size >12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.
5. Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
6. Scar or fibrosis making up >50% of the total lesion in the study eye.
7. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
9. History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
10. Presence of other causes of CNV in the study eye.
11. Prior vitrectomy in the study eye.
12. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
13. Any history of macular hole of stage 2 and above in the study eye.
14. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
15. History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Gender Both
Minimum age 50 Years
Healthy volunteers No

Administrative Data

Organization name	Bayer
Organization study ID	91689
Secondary ID	EurdaCT No.: 2007-000583-25
Secondary ID	311523
Secondary ID	VIEW 2
Sponsor	Bayer
Collaborator	Regeneron Pharmaceuticals
Health Authority	Switzerland: Ethikkommision

OBS 3

REGENERON PHARMACEUTICALS INC

FORM 10-Q
(Quarterly Report)

Filed 11/07/07 for the Period Ending 09/30/07

Address	777 OLD SAW MILL RIVER RD TARRYTOWN, NY 10591-6707
Telephone	9143477000
CIK	0000872589
Symbol	REGN
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-Q

(Mark One)

☑ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended September 30, 2007

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15 (d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission File Number 0-19034

REGENERON PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

New York	13-3444607
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
777 Old Saw Mill River Road Tarrytown, New York	10591-6707
(Address of principal executive offices)	(Zip Code)

(914) 347-7000
(Registrant's telephone number, including area code)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☑ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☑ Non-accelerated filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ☐ No ☑

Indicate the number of shares outstanding of each of the issuer's classes of common stock as of October 31, 2007:

Class of Common Stock	Number of Shares
Class A Stock, $0.001 par value	2,260,266
Common Stock, $0.001 par value	63,889,481

REGENERON PHARMACEUTICALS, INC.
Table of Contents
September 30, 2007

PART I. FINANCIAL INFORMATION
ITEM 1. FINANCIAL STATEMENTS

REGENERON PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS AT SEPTEMBER 30, 2007 AND DECEMBER 31, 2006 (Unaudited)
(In thousands, except share data)

	September 30, 2007	December 31, 2006
ASSETS		
Current assets		
Cash and cash equivalents	$ 97,416	$ 237,876
Marketable securities	299,566	221,400
Accounts receivable	10,968	7,493
Prepaid expenses and other current assets	14,070	3,215
Total current assets	422,020	469,984
Restricted cash	1,600	1,600
Marketable securities	98,710	61,983
Property, plant, and equipment, at cost, net of accumulated depreciation and amortization	49,358	49,353
Other assets	1,408	2,170
Total assets	$ 573,096	$ 585,090
LIABILITIES and STOCKHOLDERS' EQUITY		
Current liabilities		
Accounts payable and accrued expenses	$ 27,872	$ 21,471
Deferred revenue, current portion	68,814	23,543
Total current liabilities	96,686	45,014
Deferred revenue	125,013	123,452
Notes payable	200,000	200,000
Total liabilities	421,699	368,466
Commitments and contingencies		
Stockholders' equity		
Preferred stock, $.01 par value; 30,000,000 shares authorized; issued and outstanding-none		
Class A Stock, convertible, $.001 par value; 40,000,000 shares authorized; shares issued and outstanding - 2,260,266 in 2007 and 2,270,353 in 2006	2	2
Common Stock, $.001 par value; 160,000,000 shares authorized; shares issued and outstanding - 63,825,329 in 2007 and 63,130,962 in 2006	64	63
Additional paid-in capital	931,482	904,407
Accumulated deficit	(780,146)	(687,617)
Accumulated other comprehensive loss	(5)	(231)
Total stockholders' equity	151,397	216,624
Total liabilities and stockholders' equity	$ 573,096	$ 585,090

The accompanying notes are an integral part of the financial statements.

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

	Three months ended September 30,		Nine months ended September 30,	
	2007	2006	2007	2006
Revenues				
Contract research and development	$ 12,311	$ 11,448	$ 41,873	$ 41,026
Contract manufacturing		4,176		12,075
Technology licensing	10,000		18,421	
	22,311	15,624	60,294	53,101
Expenses				
Research and development	51,689	34,808	136,788	101,290
Contract manufacturing		3,054		7,716
General and administrative	9,289	6,019	26,426	18,264
	60,978	43,881	163,214	127,270
Loss from operations	(38,667)	(28,257)	(102,920)	(74,169)
Other income (expense)				
Investment income	5,840	3,858	19,424	11,023
Interest expense	(3,011)	(3,011)	(9,033)	(9,033)
	2,829	847	10,391	1,990
Net loss before cumulative effect of a change in accounting principle	(35,838)	(27,410)	(92,529)	(72,179)
Cumulative effect of adopting Statement of Financial Accounting Standards No. 123R ("SFAS 123R")				813
Net loss	$ (35,838)	$ (27,410)	$ (92,529)	$ (71,366)
Net loss per share amounts, basic and diluted:				
Net loss before cumulative effect of a change in accounting principle	$ (0.54)	$ (0.48)	$ (1.40)	$ (1.27)
Cumulative effect of adopting SFAS 123R				0.02
Net loss	$ (0.54)	$ (0.48)	$ (1.40)	$ (1.25)
Weighted average shares outstanding, basic and diluted	66,069	57,011	65,861	56,884

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENT OF STOCKHOLDERS' EQUITY (Unaudited)
For the nine months ended September 30, 2007
(In thousands)

	Class A Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total Stockholders' Equity	Comprehensive Loss
	Shares	Amount	Shares	Amount					
Balance, December 31, 2006	2,270	$ 2	63,131	$ 63	$ 904,407	$ (687,617)	$ (231)	$ 216,624	
Issuance of Common Stock in connection with exercise of stock options, net of shares tendered			619	1	5,170			5,171	
Issuance of Common Stock in connection with Company 401(k) Savings Plan contribution			65		1,367			1,367	
Conversion of Class A Stock to Common Stock	(10)		10						
Stock-based compensation expense					20,538			20,538	
Net loss						(92,529)		(92,529)	$ (92,529)
Change in net unrealized loss on marketable securities							226	226	226
Balance, September 30, 2007	2,260	$ 2	63,825	$ 64	$ 931,482	$ (780,146)	$ (5)	$ 151,397	$ (92,303)

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF CASH FLOWS (Unaudited)
(In thousands)

	Nine months ended September 30, 2007	2006
Cash flows from operating activities		
Net loss	$ (92,529)	$ (71,366)
Adjustments to reconcile net loss to net cash used in operating activities		
Depreciation and amortization	8,588	11,196
Non-cash compensation expense	20,538	13,542
Impairment charge on marketable securities	803	
Cumulative effect of a change in accounting principle		(813)
Changes in assets and liabilities		
(Increase) decrease in accounts receivable	(3,475)	28,581
(Increase) decrease in prepaid expenses and other assets	(11,876)	364
Decrease in inventory		3,524
Increase (decrease) in deferred revenue	46,832	(12,503)
Increase (decrease) in accounts payable, accrued expenses, and other liabilities	7,674	(2,753)
Total adjustments	69,084	41,138
Net cash used in operating activities	(23,445)	(30,228)
Cash flows from investing activities		
Purchases of marketable securities	(478,209)	(252,037)
Sales or maturities of marketable securities	363,739	261,749
Capital expenditures	(7,716)	(1,603)
Net cash (used in) provided by investing activities	(122,186)	8,109
Cash flows from financing activities		
Net proceeds from the issuance of Common Stock	5,171	4,883
Other		390
Net cash provided by financing activities	5,171	5,273
Net decrease in cash and cash equivalents	(140,460)	(16,846)
Cash and cash equivalents at beginning of period	237,876	184,508
Cash and cash equivalents at end of period	$ 97,416	$ 167,662

The accompanying notes are an integral part of the financial statements.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

1. Interim Financial Statements

The interim Condensed Financial Statements of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company") have been prepared in accordance with the instructions to Form 10-Q and Article 10 of Regulation S-X. Accordingly, they do not include all information and disclosures necessary for a presentation of the Company's financial position, results of operations, and cash flows in conformity with accounting principles generally accepted in the United States of America. In the opinion of management, these financial statements reflect all adjustments, consisting only of normal recurring accruals, necessary for a fair presentation of the Company's financial position, results of operations, and cash flows for such periods. The results of operations for any interim periods are not necessarily indicative of the results for the full year. The December 31, 2006 Condensed Balance Sheet data were derived from audited financial statements, but do not include all disclosures required by accounting principles generally accepted in the United States of America. These financial statements should be read in conjunction with the financial statements and notes thereto contained in the Company's Annual Report on Form 10-K for the year ended December 31, 2006.

2. Per Share Data

The Company's basic and diluted net loss per share amounts have been computed by dividing net loss by the weighted average number of shares of Common Stock and Class A Stock outstanding. Net loss per share is presented on a combined basis, inclusive of Common Stock and Class A Stock outstanding, as each class of stock has equivalent economic rights. For the three and nine months ended September 30, 2007 and 2006, the Company reported net losses; therefore, no common stock equivalents were included in the computation of diluted net loss per share for these periods, since such inclusion would have been antidilutive. The calculations of basic and diluted net loss per share are as follows:

	Three Months Ended September 30,	
	2007	2006
Net loss (Numerator)	$(35,838)	$(27,410)
Weighted-average shares, in thousands (Denominator)	66,069	57,011
Basic and diluted net loss per share	$ (0.54)	$ (0.48)

	Nine Months Ended September 30,	
	2007	2006
Net loss (Numerator)	$(92,529)	$(71,366)
Weighted-average shares, in thousands (Denominator)	65,861	56,884
Basic and diluted net loss per share	$ (1.40)	$ (1.25)

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

Shares issuable upon the exercise of stock options, vesting of restricted stock awards, and conversion of convertible debt, which have been excluded from the September 30, 2007 and 2006 diluted per share amounts because their effect would have been antidilutive, include the following:

	Three months ended September 30,	
	2007	2006
Stock Options:		
Weighted average number, in thousands	15,153	14,082
Weighted average exercise price	$ 16.01	$ 14.35
Convertible Debt:		
Weighted average number, in thousands	6,611	6,611
Conversion price	$ 30.25	$ 30.25

	Nine months ended September 30,	
	2007	2006
Stock Options:		
Weighted average number, in thousands	15,308	14,220
Weighted average exercise price	$ 15.86	$ 14.31
Restricted Stock:		
Weighted average number, in thousands	—	31
Convertible Debt:		
Weighted average number, in thousands	6,611	6,611
Conversion price	$ 30.25	$ 30.25

3. Statement of Cash Flows

Supplemental disclosure of noncash investing and financing activities:

Included in accounts payable and accrued expenses at September 30, 2007 and December 31, 2006 are $0.9 million and $0.8 million, respectively, of accrued capital expenditures. Included in accounts payable and accrued expenses at September 30, 2006 and December 31, 2005 are $0.4 million and $0.2 million, respectively, of accrued capital expenditures.

Included in accounts payable and accrued expenses at December 31, 2006 and 2005 are $1.4 million and $1.9 million, respectively, of accrued Company 401(k) Savings Plan contribution expense. In the first quarter of 2007 and 2006, the Company contributed 64,532 and 120,960 shares, respectively, of Common Stock to the 401(k) Savings Plan in satisfaction of these obligations.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

Included in marketable securities at September 30, 2007 and December 31, 2006 are $2.5 million and $1.5 million, respectively, of accrued interest income. Included in marketable securities at September 30, 2006 and December 31, 2005 are $0.4 million and $1.2 million, respectively, of accrued interest income.

4. Accounts Receivable

Accounts receivable as of September 30, 2007 and December 31, 2006 consist of the following:

	September 30, 2007	December 31, 2006
Receivable from the sanofi-aventis Group	$ 7,075	$ 6,900
Receivable from National Institutes of Health	2,227	549
Receivable from Bayer HealthCare LLC	1,387	
Other	279	44
	$ 10,968	$ 7,493

5. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses as of September 30, 2007 and December 31, 2006 consist of the following:

	September 30, 2007	December 31, 2006
Accounts payable	$ 5,330	$ 4,349
Accrued payroll and related costs	7,837	9,932
Accrued clinical trial expense	5,084	2,606
Accrued expenses, other	4,579	2,292
Interest payable on convertible notes	5,042	2,292
	$ 27,872	$ 21,471

6. Comprehensive Loss

Comprehensive loss represents the change in net assets of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss of the Company includes net loss adjusted for the change in net unrealized gain (loss) on marketable securities. The net effect of income taxes on comprehensive loss is immaterial. For the three and nine months ended September 30, 2007 and 2006, the components of comprehensive loss are:

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

	Three months ended September 30,	
	2007	2006
Net loss	$(35,838)	$(27,410)
Change in net unrealized gain (loss) on marketable securities	511	378
Total comprehensive loss	$(35,327)	$(27,032)

	Nine months ended September 30,	
	2007	2006
Net loss	$(92,529)	$(71,366)
Change in net unrealized gain (loss) on marketable securities	226	375
Total comprehensive loss	$(92,303)	$(70,991)

7. Accounting for Collaboration with Bayer HealthCare

In October 2006, the Company entered into a license and collaboration agreement with Bayer HealthCare LLC to globally develop and commercialize outside the United States the Company's VEGF Trap for the treatment of eye disease by local administration ("VEGF Trap-Eye"). Under the terms of the agreement, Bayer made a non-refundable up-front payment to the Company of $75.0 million. In 2007, agreed upon VEGF Trap-Eye development expenses incurred by both companies under a global development plan will be shared as follows: Up to the first $50.0 million will be shared equally; Regeneron is solely responsible for the next $40.0 million; over $90.0 million will be shared equally. Through September 30, 2007, reimbursements from Bayer HealthCare of the Company's VEGF Trap-Eye development expenses totaled $12.9 million, of which $1.4 million was receivable at September 30, 2007. Neither party was reimbursed for any development expenses that it incurred prior to 2007. In addition, in August 2007, the Company received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in the neovascular form of age-related macular degeneration ("wet AMD").

The Company and Bayer HealthCare are currently formalizing the global development plans for the VEGF Trap-Eye in wet AMD and diabetic macular edema. The plans will include estimated development steps, timelines, and costs, as well as the projected responsibilities of and costs to be incurred by each of the companies. Pending completion of these plans, all payments received or receivable by the Company from Bayer HealthCare through September 30, 2007, totaling $107.9 million, have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, the Company will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in the Company's Statement of Operations. In the period when the Company commences recognizing previously deferred payments from Bayer HealthCare, the Company anticipates recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

8. 2007 License Agreements

AstraZeneca

In February 2007, the Company entered into a non-exclusive license agreement with AstraZeneca UK Limited that allows AstraZeneca to utilize the Company's *VelocImmune* ® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, AstraZeneca made a $20.0 million non-refundable up-front payment to the Company which was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. AstraZeneca also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. These additional payments will be recognized as revenue ratably over their respective annual license periods. The Company is entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by AstraZeneca using the Company's *VelocImmune* technology. For the nine months ended September 30, 2007, the Company recognized $12.1 million of revenue in connection with the AstraZeneca license agreement. At September 30, 2007, deferred revenue was $7.9 million.

Astellas

In March 2007, the Company entered into a non-exclusive license agreement with Astellas Pharma Inc. that allows Astellas to utilize the Company's *VelocImmune* technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, Astellas made a $20.0 million non-refundable up-front payment to the Company, which was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. Astellas also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. These additional payments will be recognized as revenue ratably over their respective annual license periods. The Company is entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by Astellas using the Company's *VelocImmune* technology. For the nine months ended September 30, 2007, the Company recognized $6.3 million of revenue in connection with the Astellas license agreement. At September 30, 2007, deferred revenue was $13.7 million.

9. Income Taxes

Effective January 1, 2007, the Company adopted the provisions of Financial Accounting Standards Board ("FASB") Interpretation No. 48 ("FIN 48"), *Accounting for Uncertainty in Income Taxes — an interpretation of FASB Statement No. 109.* The implementation of FIN 48 had

no impact on the Company's financial statements as the Company has no unrecognized tax benefits.

The Company is primarily subject to U.S. federal and New York State income tax. The Company's 1992 and subsequent tax years remain open to examination by U.S. federal and state tax authorities.

The Company's policy is to recognize interest and penalties related to income tax matters in income tax expense. As of January 1 and September 30, 2007, the Company had no accruals for interest or penalties related to income tax matters.

10. Legal Matters

From time to time, the Company is a party to legal proceedings in the course of the Company's business. The Company does not expect any such current legal proceedings to have a material adverse effect on the Company's business or financial condition.

11. Segment Information

Through 2006, the Company's operations were managed in two business segments: research and development, and contract manufacturing.

Research and development: Includes all activities related to the discovery of pharmaceutical products for the treatment of serious medical conditions, and the development and commercialization of these discoveries. Also includes revenues and expenses related to activities conducted under contract research and technology licensing agreements.

Contract manufacturing: Includes all revenues and expenses related to the commercial production of products under contract manufacturing arrangements. During 2006, the Company produced a vaccine intermediate for Merck & Co., Inc. under a manufacturing agreement, which expired in October 2006.

Due to the expiration of the Company's manufacturing agreement with Merck in October 2006, beginning in 2007, the Company only has a research and development business segment. Therefore, segment information has not been provided for 2007 in the table below.

The following table presents information about reported segments for the three and nine months ended September 30, 2006.

REGENERON PHARMACEUTICALS, INC.
Notes to Condensed Financial Statements (Unaudited)
(Unless otherwise noted, dollars in thousands, except per share data)

	Three months ended September 30, 2006			
	Research & Development	Contract Manufacturing	Reconciling Items	Total
Revenues	$ 11,448	$ 4,176	—	$ 15,624
Depreciation and amortization	3,447	—(1)	$ 261	3,708
Non-cash compensation expense	4,632	130	—	4,762
Interest expense	—	—	3,011	3,011
Net (loss) income	(29,379)	1,122	847(2)	(27,410)
Capital expenditures	441	—	—	441

	Nine months ended September 30, 2006			
	Research & Development	Contract Manufacturing	Reconciling Items	Total
Revenues	$ 41,026	$12,075	—	$ 53,101
Depreciation and amortization	10,413	—(1)	$ 783	11,196
Non-cash compensation expense	13,220	322	(813) (3)	12,729
Interest expense	—	—	9,033	9,033
Net (loss) income	(78,528)	4,359	2,803(2)	(71,366)
Capital expenditures	1,409	—	—	1,409
Total assets	57,530	1,445	296,211(4)	355,186

(1) Depreciation and amortization related to contract manufacturing was capitalized into inventory and included in contract manufacturing expense when the product was shipped.

(2) Represents investment income, net of interest expense related primarily to convertible notes issued in October 2001. For the nine months ended September 30, 2006, also includes the cumulative effect of adopting Statement of Financial Accounting Standards No. ("SFAS") 123R, *Share-Based Payment.*

(3) Represents the cumulative effect of adopting SFAS 123R.

(4) Includes cash and cash equivalents, marketable securities, restricted cash (where applicable), prepaid expenses and other current assets, and other assets.

12. Future Impact of Recently Issued Accounting Standards

In February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities* . SFAS 159 permits entities to choose to measure many financial instruments and certain other items at fair value. The objective is to improve financial reporting by providing entities with the opportunity to mitigate volatility in reported earnings caused by measuring related assets and liabilities differently without having to apply complex hedge accounting provisions. SFAS 159 is effective for financial statements issued for fiscal years beginning after November 15, 2007. The Company will be required to adopt SFAS 159 effective

for the fiscal year beginning January 1, 2008. Management is currently evaluating the potential impact of adopting SFAS 159 on the Company's financial statements.

In June 2007, the Emerging Issues Task Force issued Statement No. 07-3, *Accounting for Non-refundable Advance Payments for Goods or Services to Be Used in Future Research and Development Activities* ("EITF 07-3"). EITF 07-3 addresses how entities involved in research and development activities should account for the non-refundable portion of an advance payment made for future research and development activities and requires that such payments be deferred and capitalized, and recognized as an expense when the goods are delivered or the related services are performed. EITF 07-3 is effective for fiscal years beginning after December 15, 2007, including interim periods within those fiscal years. The Company will be required to adopt EITF 07-3 effective for the fiscal year beginning January 1, 2008. Management believes that the future adoption of EITF 07-3 will not have a material impact on the Company's financial statements.

13. Subsequent Events

Purchase of Building – Rensselaer, New York

In June 2007, the Company exercised a purchase option on a building in Rensselaer, New York, in which the Company leased manufacturing, office, and warehouse space in a portion of the building. The Company completed the purchase of this property (land and building) in October 2007 at a cost of approximately $9 million.

Amendment to Operating Lease – Tarrytown, New York Facilities

The Company leases laboratory and office facilities in Tarrytown, New York. In December 2006, the Company entered into a new agreement to lease laboratory and office space that is now under construction and expected to be completed in mid-2009 at the Company's current Tarrytown location, plus retain a portion of the Company's existing space. In October 2007, the Company amended the December 2006 operating lease agreement to increase the amount of new space the Company will lease. The term of the lease is now expected to commence in mid-2008 and will expire approximately 16 years later. Other terms and conditions, as previously described in the Company's Form 10-K for the year ended December 31, 2006, remain unchanged.

In connection with these two subsequent events, the Company's previously disclosed total estimated future minimum noncancelable lease commitments under operating leases, as per the Company's Form 10-K for the year ended December 31, 2006, will decrease to $4.6 million and $9.3 million for the years ended December 31, 2008 and 2009, respectively, and increase to $14.2 million and $14.4 million for the years ended December 31, 2010 and 2011, respectively, and to $204.2 million, in the aggregate, for years subsequent to 2011.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The discussion below contains forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron Pharmaceuticals, Inc. and actual events or results may differ materially. These statements concern, among other things, the possible success and therapeutic applications of our product candidates and research programs, the timing and nature of the clinical and research programs now underway or planned, and the future sources and uses of capital and our financial needs. These statements are made by us based on management's current beliefs and judgment. In evaluating such statements, stockholders and potential investors should specifically consider the various factors identified under the caption "Risk Factors" which could cause actual results to differ materially from those indicated by such forward-looking statements. We do not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required by law.

Overview

Regeneron Pharmaceuticals, Inc. is a biopharmaceutical company that discovers, develops, and intends to commercialize pharmaceutical products for the treatment of serious medical conditions. We are currently focused on three development programs: rilonacept (IL-1 Trap) in various inflammatory indications, aflibercept (VEGF Trap) in oncology and the VEGF Trap-Eye formulation in eye diseases using intraocular delivery. Aflibercept is being developed in oncology in collaboration with the sanofi-aventis Group. The VEGF Trap-Eye is being developed in collaboration with Bayer HealthCare LLC. Our preclinical research programs are in the areas of oncology and angiogenesis, ophthalmology, metabolic and related diseases, muscle diseases and disorders, inflammation and immune diseases, bone and cartilage, pain, and cardiovascular diseases. We expect that our next generation of product candidates will be based on our proprietary technologies for developing human monoclonal antibodies. Developing and commercializing new medicines entails significant risk and expense. Since inception, we have not generated any sales or profits from the commercialization of any of our product candidates.

Our core business strategy is to maintain a strong foundation in basic scientific research and discovery-enabling technology and combine that foundation with our manufacturing and clinical development capabilities to build a successful, integrated biopharmaceutical company. We believe that our ability to develop product candidates is enhanced by the application of our technology platforms. Our discovery platforms are designed to identify specific genes of therapeutic interest for a particular disease or cell type and validate targets through high-throughput production of mammalian models. Our human monoclonal antibody technology (*VelocImmune* ®) and cell line expression technologies may then be utilized to design and produce new product candidates directed against the disease target. Based on the *VelocImmune* platform which we believe, in conjunction with our other proprietary technologies, can accelerate the development of fully human monoclonal antibodies, we plan to move our first new antibody product candidate into clinical trials in the fourth quarter of 2007. We plan to introduce two new antibody product candidates into clinical development each year, beginning in 2008. We continue to invest in the development of enabling technologies to assist in our efforts to identify, develop, and commercialize new product candidates.

Clinical Programs:

Below is a summary of the status of our clinical candidates:

1. Rilonacept – Inflammatory Diseases

Rilonacept (IL-1 Trap) is a protein-based product candidate designed to bind the interleukin-1 (called IL-1) cytokine and prevent its interaction with cell surface receptors. We are evaluating rilonacept in a number of diseases and disorders where IL-1 may play an important role, including a group of rare diseases called Cryopyrin-Associated Periodic Syndromes (CAPS) and other diseases associated with inflammation.

We recently submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for rilonacept in CAPS. In August 2007, the FDA granted priority review status to the BLA for rilonacept for the long-term treatment of CAPS. The FDA previously granted Orphan Drug status and Fast Track designation to rilonacept for the treatment of CAPS. In July 2007, rilonacept also received Orphan Drug designation in the European Union for the treatment of CAPS. In November 2007, we announced that we received notification from the FDA that the action date for the FDA's priority review of the BLA for rilonacept had been extended three months to February 29, 2008.

CAPS represents a group of rare inherited auto-inflammatory conditions, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). CAPS also includes Neonatal Onset Multisystem Inflammatory Disease (NOMID). Rilonacept has not been studied, and is not expected to be indicated, for the treatment of NOMID. The syndromes included in CAPS are characterized by spontaneous, systemic inflammation and are termed auto-inflammatory disorders. A novel feature of these conditions (particularly FCAS and MWS) is that exposure to mild degrees of cold temperature can provoke a major inflammatory episode that occurs within hours. CAPS is caused by a range of mutations in the gene *CIAS1* (also known as NLRP3) which encodes a protein named cryopyrin. Currently, there are no medicines approved for the treatment of CAPS.

We recently reported positive results from an exploratory proof of concept study of rilonacept in ten patients with chronic active gout. In those patients, treatment with rilonacept demonstrated a statistically significant reduction in patient pain scores in the single-blind, placebo-controlled study. Mean patients' pain scores, the key symptom measure in persistent gout, were reduced 41% ($p=0.025$) during the first two weeks of active treatment and reduced 56% ($p<0.004$) after six weeks of active treatment. In this study, in which safety was the primary endpoint measure, treatment with rilonacept was generally well-tolerated. We have initiated a Phase 2 safety and efficacy trial of rilonacept in the prevention of gout flares induced by the initiation of uric acid-lowering drug therapy used to control the disease.

We are also evaluating the potential use of rilonacept in other indications in which IL-1 may play a role, and are preparing to initiate exploratory proof-of-concept studies in anemia and other indications. The first of these studies will be in the treatment of anemia associated with chronic inflammation, which we plan to begin in the fourth quarter of 2007.

Under a March 2003 collaboration agreement with Novartis Pharma AG, we retain the right to elect to collaborate in the future development and commercialization of a Novartis IL-1 antibody, which is in clinical development. Following completion of Phase 2 development and submission to us of a written report on the Novartis IL-1 antibody, we have the right, in consideration for an opt-in payment, to elect to co-develop and co-commercialize the Novartis IL-1 antibody in North America. If we elect to exercise this right, we are responsible for paying 45% of post-election North American development costs for the antibody product. In return, we are entitled to co-promote the Novartis IL-1 antibody and to receive 45% of net profits on sales of the antibody product in North America. Under certain circumstances, we are also entitled to receive royalties on sales of the Novartis IL-1 antibody in Europe.

Under the collaboration agreement, Novartis has the right to elect to collaborate in the development and commercialization of a second generation rilonacept following completion of its Phase 2 development, should we decide to clinically develop such a second generation product candidate. Novartis does not have any rights or options with respect to our rilonacept currently in clinical development.

2. Aflibercept (VEGF Trap) – Oncology

Aflibercept is a protein-based product candidate designed to bind all forms of Vascular Endothelial Growth Factor-A (called VEGF-A, also known as Vascular Permeability Factor or VPF) and the related Placental Growth Factor (called PlGF), and prevent their interaction with cell surface receptors. VEGF-A (and to a less validated degree, PlGF) is required for the growth of new blood vessels that are needed for tumors to grow and is a potent regulator of vascular permeability and leakage.

Aflibercept is being developed in cancer indications in collaboration with sanofi-aventis. We and sanofi-aventis began the first two trials of our global Phase 3 development program in the third quarter of 2007. One trial will evaluate aflibercept in combination with docetaxel/prednisone in patients with 1 st line metastatic androgen independent prostate cancer. The other trial will evaluate aflibercept in combination with docetaxel in patients with 2 nd line metastatic non-small cell lung cancer. The companies plan to initiate two additional Phase 3 trials before the end of 2007 in first-line metastatic pancreatic cancer in combination with gemcitabine-based regimen and second-line metastatic colorectal cancer in combination with FOLFIRI (Folinic Acid (leucovorin), 5-fluorouracil, and irinotecan). In all of these trials, aflibercept is being combined with the current standard of chemotherapy care for the stated development stage of the cancer type.

The collaboration is conducting a number of other trials in the global development program for aflibercept. Five safety and tolerability studies of aflibercept in combination with standard chemotherapy regimens are continuing in a variety of cancer types to support the Phase 3 clinical program. Sanofi-aventis has also expanded the development program to Japan, where they are conducting a Phase 1 safety and tolerability study in combination with S-1 in patients with advanced solid malignancies.

The collaboration is also conducting Phase 2 single-agent studies in advanced ovarian cancer (AOC), non-small cell lung adenocarcinoma (NSCLA), and AOC patients with symptomatic malignant ascites (SMA). The AOC and NSCLA trials are fully enrolled and ongoing. The

SMA trial is approximately 50% enrolled and continues to enroll patients. In 2004, the FDA granted Fast Track designation to aflibercept for the treatment of SMA.

In addition, currently underway or scheduled to begin are more than 10 studies to be conducted in conjunction with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) evaluating aflibercept as a single agent or in combination with chemotherapy regimens in a variety of cancer indications.

The development program in oncology is expected to total over $400 million over the next several years. These expenses will be funded by sanofi-aventis in accordance with the terms of our collaboration agreement described below.

The first registration submission to a regulatory agency for aflibercept is possible as early as 2008, potentially as third line treatment as a single agent in advanced ovarian cancer (AOC). However, in order for our ongoing Phase 2 study in AOC to be sufficient to support such a submission, we believe that the final unblinded results of the study would have to demonstrate a more robust response rate than that reported in the interim analysis of blinded data from the study presented in June 2007 at the annual meeting of the American Society of Clinical Oncology (ASCO).

Cancer is a heterogeneous set of diseases and one of the leading causes of death in the developed world. A mutation in any one of dozens of normal genes can eventually result in a cell becoming cancerous; however, a common feature of cancer cells is that they need to obtain nutrients and remove waste products, just as normal cells do. The vascular system normally supplies nutrients to and removes waste from normal tissues. Cancer cells can use the vascular system either by taking over preexisting blood vessels or by promoting the growth of new blood vessels (a process known as angiogenesis). VEGF is secreted by many tumors to stimulate the growth of new blood vessels to supply nutrients and oxygen to the tumor. VEGF blockers have been shown to inhibit new vessel growth; and, in some cases, can cause regression of existing tumor vasculature. Countering the effects of VEGF, thereby blocking the blood supply to tumors, has demonstrated therapeutic benefits in clinical trials. This approach of inhibiting angiogenesis as a mechanism of action for an oncology medicine was validated in February 2004, when the FDA approved Genentech, Inc.'s VEGF inhibitor, Avastin ®. Avastin ® (a trademark of Genentech, Inc.) is an antibody product designed to inhibit VEGF and interfere with the blood supply to tumors.

Collaboration with the sanofi-aventis Group

In September 2003, we entered into a collaboration agreement with Aventis Pharmaceuticals, Inc. (predecessor to sanofi-aventis U.S.) to collaborate on the development and commercialization of aflibercept in all countries other than Japan, where we retained the exclusive right to develop and commercialize aflibercept. In January 2005, we and sanofi-aventis amended the collaboration agreement to exclude, from the scope of the collaboration, the development and commercialization of aflibercept for intraocular delivery to the eye. In December 2005, we and sanofi-aventis amended our collaboration agreement to expand the territory in which the companies are collaborating on the development of aflibercept to include Japan. Under the collaboration agreement, as amended, we and sanofi-aventis will share co-promotion rights and profits on sales, if any, of aflibercept outside of Japan for disease

indications included in our collaboration. In Japan, we are entitled to a royalty of approximately 35% on annual sales of aflibercept, subject to certain potential adjustments. We may also receive up to $400.0 million in milestone payments upon receipt of specified marketing approvals. This total includes up to $360.0 million in milestone payments related to receipt of marketing approvals for up to eight aflibercept oncology and other indications in the United States or the European Union. Another $40.0 million of milestone payments relate to receipt of marketing approvals for up to five oncology indications in Japan.

Under the collaboration agreement, as amended, agreed upon worldwide development expenses incurred by both companies during the term of the agreement will be funded by sanofi-aventis. If the collaboration becomes profitable, we will be obligated to reimburse sanofi-aventis for 50% of aflibercept development expenses in accordance with a formula based on the amount of development expenses and our share of the collaboration profits and Japan royalties, or at a faster rate at our option.

3. VEGF Trap – Eye Diseases

The VEGF Trap-Eye is a form of the VEGF Trap that has been purified and formulated with excipients and at concentrations suitable for direct injection into the eye. The VEGF Trap-Eye currently is being tested in a Phase 3 trial in patients with the neovascular form of age-related macular degeneration (wet AMD) and has completed a small pilot study in patients with diabetic macular edema (DME).

In the clinical development program for the VEGF Trap-Eye, we and Bayer HealthCare have initiated a Phase 3 study of the VEGF Trap-Eye in wet AMD. This first trial, known as VIEW 1 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), is comparing the VEGF Trap-Eye and Genentech, Inc.'s Lucentis ® (ranibizumab), an anti-angiogenic agent approved for use in wet AMD. This Phase 3 trial is evaluating dosing intervals of four and eight weeks for the VEGF Trap-Eye compared with ranibizumab dosed according to its label every four weeks. We and Bayer HealthCare plan to initiate a second Phase 3 trial in wet AMD in the first quarter of 2008. This second trial will be conducted primarily in the European Union and other parts of the world outside the U.S.

In October 2007, we and Bayer HealthCare announced positive results from the full analysis of the primary 12-week endpoint of a Phase 2 study evaluating the VEGF Trap-Eye in wet AMD. The VEGF Trap-Eye met the primary study endpoint of a statistically significant reduction in retinal thickness, a measure of disease activity, after 12 weeks of treatment compared with baseline (all five dose groups combined, mean decrease of 119 microns, $p<0.0001$). The mean change from baseline in visual acuity, a key secondary endpoint of the study, also demonstrated statistically significant improvement (all groups combined, increase of 5.7 letters, $p<0.0001$). Preliminary analyses at 16 weeks showed that the VEGF Trap-Eye, dosed monthly, achieved a mean gain in visual acuity of 9.3 to 10 letters (for the 0.5 and 2 mg dose groups, respectively). In additional exploratory analyses, the VEGF Trap-Eye, dosed monthly, reduced the proportion of patients with vision of 20/200 or worse (a generally accepted definition for legal blindness) from 14.3% at baseline to 1.6% at week 16; the proportion of patients with vision of 20/40 or better (part of the legal minimum requirement for an unrestricted driver's license in the U.S.) was likewise increased from 19.0% at baseline to 49.2% at 16 weeks. These findings were presented at the Retina Society Conference.

We and Bayer HealthCare are also developing the VEGF Trap-Eye in DME and expect to initiate a Phase 3 study in DME in mid-2008. In May 2007, at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), the companies reported results from a small pilot study of the VEGF Trap-Eye in patients with DME. In the study, the VEGF Trap-Eye was well tolerated and demonstrated activity in five patients, with decreases in retinal thickness and improvement in visual acuity.

VEGF-A both stimulates angiogenesis and increases vascular permeability. It has been shown in preclinical studies to be a major pathogenic factor in both wet AMD and diabetic retinopathy, and it is believed to be involved in other medical problems affecting the eyes. In clinical trials, blocking VEGF-A has been shown to be effective in patients with wet AMD, and Macugen ® (OSI Pharmaceuticals, Inc.) and Lucentis ® (Genentech, Inc.) have been approved to treat patients with this condition.

Wet AMD and diabetic retinopathy (DR) are two of the leading causes of adult blindness in the developed world. In both conditions, severe visual loss is caused by a combination of retinal edema and neovascular proliferation. DR is a major complication of diabetes mellitus that can lead to significant vision impairment. DR is characterized, in part, by vascular leakage, which results in the collection of fluid in the retina. When the macula, the central area of the retina that is responsible for fine visual acuity, is involved, loss of visual acuity occurs. This is referred to as diabetic macular edema (DME). DME is the most prevalent cause of moderate visual loss in patients with diabetes.

Collaboration with Bayer HealthCare LLC

In October 2006, we entered into a collaboration agreement with Bayer HealthCare for the global development and commercialization outside the United States of the VEGF Trap-Eye. Under the agreement, we and Bayer HealthCare will collaborate on, and share the costs of, the development of the VEGF Trap-Eye through an integrated global plan that encompasses wet AMD, diabetic eye diseases, and other diseases and disorders. Bayer HealthCare will market the VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of the VEGF Trap-Eye. If the VEGF Trap-Eye is granted marketing authorization in a major market country outside the United States, we will be obligated to reimburse Bayer HealthCare for 50% of the development costs that it has incurred under the agreement from our share of the collaboration profits. Within the United States, we retained exclusive commercialization rights to the VEGF Trap-Eye and are entitled to all profits from any such sales. We received an up-front payment of $75.0 million from Bayer HealthCare. In August 2007, we received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in wet AMD, and can earn up to $90.0 million in additional development and regulatory milestones related to the development of the VEGF Trap-Eye and marketing approvals in major market countries outside the United States. We can also earn up to $135.0 million in sales milestones if total annual sales of the VEGF Trap-Eye outside the United States achieve certain specified levels starting at $200.0 million.

General

Developing and commercializing new medicines entails significant risk and expense. Since inception we have not generated any sales or profits from the commercialization of any of our product candidates and may never receive such revenues. Before revenues from the commercialization of our product candidates can be realized, we (or our collaborators) must overcome a number of hurdles which include successfully completing research and development and obtaining regulatory approval from the FDA and regulatory authorities in other countries. In addition, the biotechnology and pharmaceutical industries are rapidly evolving and highly competitive, and new developments may render our products and technologies uncompetitive or obsolete.

From inception on January 8, 1988 through September 30, 2007, we had a cumulative loss of $780.1 million. In the absence of revenues from the commercialization of our product candidates or other sources, the amount, timing, nature, and source of which cannot be predicted, our losses will continue as we conduct our research and development activities. We expect to incur substantial losses over the next several years as we continue the clinical development of the VEGF Trap-Eye and rilonacept; advance new product candidates into clinical development from our existing research programs utilizing our technology for designing fully human monoclonal antibodies; continue our research and development programs; and commercialize product candidates that receive regulatory approval, if any. Also, our activities may expand over time and require additional resources, and we expect our operating losses to be substantial over at least the next several years. Our losses may fluctuate from quarter to quarter and will depend on, among other factors, the progress of our research and development efforts, the timing of certain expenses, and the amount and timing of payments that we receive from collaborators.

The planning, execution, and results of our clinical programs are significant factors that can affect our operating and financial results. In our clinical programs, key events for 2007 and plans over the next 12 months are as follows:

Clinical Program	2007 Events to Date	2007-8 Plans
Rilonacept (IL-1 Trap)	• Completed the 24-week open-label safety extension phase of the Phase 3 trial in CAPS • FDA accepted BLA submission for CAPS • Granted Orphan Drug designation in CAPS in European Union • Reported positive results in exploratory proof-of-concept study in patients with chronic active gout • Initiated Phase 2 trial evaluating safety and efficacy of rilonacept in preventing gout-induced flares in patients initiating allopurinol therapy	• Receive FDA review decision to BLA submission for CAPS (expected in February 2008) • Initiate exploratory proof-of- concept study of rilonacept in a new indication • Evaluate rilonacept in other disease indications in which IL-1 may play an important role

Clinical Program	2007 Events to Date	2007-8 Plans
Aflibercept (VEGF Trap) — Oncology	• NCI/CTEP initiated more than 10 studies of the aflibercept as a single agent • Reported interim results from two Phase 2 single-agent trials – in advanced ovarian cancer and in non-small cell lung adenocarcinoma • Initiated Japanese Phase 1 trial of aflibercept in combination with S-1 in patients with solid malignancies • Sanofi-aventis initiated two Phase 3 trials of aflibercept in combination with standard chemotherapy regimens	• Sanofi-aventis to initiate two additional Phase 3 studies of aflibercept in combination with standard chemotherapy regimens in specific cancer indications • NCI/CTEP to initiate additional new exploratory safety and efficacy studies
VEGF Trap-Eye (intravitreal injection)	• Initiated first Phase 3 trial in wet AMD in patients in the U.S. and Canada • Reported positive primary endpoint results and preliminary extended treatment results of Phase 2 trial in wet AMD • Reported positive results in Phase 1 trial in DME	• Initiate second Phase 3 trial in wet AMD in the European Union and other countries around the world • Initiate Phase 3 trial in DME • Explore additional eye disease indications
VelocImmune ®		• Initiate first trial for antibody product candidate • Finalize plans to initiate clinical trials for two additional antibody candidates in 2008

License Agreements

AstraZeneca

In February 2007, we entered into a non-exclusive license agreement with AstraZeneca UK Limited that allows AstraZeneca to utilize our *VelocImmune* ® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, AstraZeneca made a $20.0 million non-refundable up-front payment to us. AstraZeneca also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. We are entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by AstraZeneca using our *VelocImmune* technology.

Astellas

In March 2007, we entered into a non-exclusive license agreement with Astellas Pharma Inc. that allows Astellas to utilize our *VelocImmune* technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, Astellas made a $20.0 million non-refundable up-front payment to us. Astellas also will make up to five additional annual payments of $20.0 million, subject to its ability to terminate the agreement after making the first three additional payments or earlier if the technology does not meet minimum performance criteria. We are entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by Astellas using our *VelocImmune* technology.

Accounting for Collaboration with Bayer HealthCare

As described above, in October 2006 we entered into a VEGF Trap-Eye license and collaboration agreement with Bayer HealthCare. Under the terms of the agreement, Bayer HealthCare made a non-refundable up-front payment to us of $75.0 million. In August 2007, we received a $20.0 million development milestone payment from Bayer HealthCare, as described above. In 2007, agreed upon VEGF Trap-Eye development expenses incurred by both companies under a global development plan will be shared as follows: Up to the first $50.0 million will be shared equally; Regeneron is solely responsible for the next $40.0 million; over $90.0 million will be shared equally. Through September 30, 2007, reimbursements from Bayer HealthCare of our VEGF Trap-Eye development expenses total $12.9 million, of which $1.4 million was receivable at September 30, 2007. Neither party was reimbursed for any development expenses that it incurred prior to 2007.

We and Bayer HealthCare are currently formalizing our global development plans for the VEGF Trap-Eye in wet AMD and DME. The plans will include estimated development steps, timelines, and costs, as well as the projected responsibilities of and costs to be incurred by each of the companies. Pending completion of these plans, all payments received or receivable from Bayer HealthCare through September 30, 2007, totaling $107.9 million, have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, we will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments from Bayer (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in our Statement of Operations. In the period when we commence recognizing previously deferred payments from Bayer HealthCare, we anticipate recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

Results of Operations

Three Months Ended September 30, 2007 and 2006

Net Loss:

Regeneron reported a net loss of $35.8 million, or $0.54 per share (basic and diluted), for the third quarter of 2007 compared to a net loss of $27.4 million, or $0.48 per share (basic and diluted), for the third quarter of 2006.

Revenues:

Revenues for the three months ended September 30, 2007 and 2006 consist of the following:

(In millions)	2007	2006	Increase (Decrease)
Contract research & development revenue			
The sanofi-aventis Group	$ 9.2	$ 10.0	$ (0.8)
Other	3.1	1.4	1.7
Total contract research & development revenue	12.3	11.4	0.9
Contract manufacturing revenue		4.2	(4.2)
Technology licensing revenue	10.0		10.0
Total revenue	$ 22.3	$ 15.6	$ 6.7

We recognize revenue from sanofi-aventis, in connection with the companies' aflibercept collaboration, in accordance with Staff Accounting Bulletin No. 104, *Revenue Recognition* (SAB 104) and FASB Emerging Issues Task Force Issue No. 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables* (EITF 00-21). We earn contract research and development revenue from sanofi-aventis which, as detailed below, consists partly of reimbursement for research and development expenses and partly of the recognition of revenue related to a total of $105.0 million of non-refundable, up-front payments received in 2003 and 2006. Non-refundable up-front license payments are recorded as deferred revenue and recognized over the period over which we are obligated to perform services. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances.

Sanofi-aventis Contract Research & Development Revenue *(In millions)*	Three months ended September 30, 2007	2006
Regeneron expense reimbursement	$ 7.0	$ 7.0
Recognition of deferred revenue related to up-front payments	2.2	3.0
Total	$ 9.2	$ 10.0

Recognition of deferred revenue related to sanofi-aventis' up-front payments decreased in the third quarter of 2007 from the same period in 2006, due to an extension of the estimated performance period over which this deferred revenue is being recognized. As of September 30, 2007, $63.2 million of the original $105.0 million of up-front payments was deferred and will be recognized as revenue in future periods.

Other contract research and development revenue includes $2.2 million and $0.1 million in the third quarters of 2007 and 2006, respectively, recognized in connection with our five-year grant from the National Institutes of Health (NIH), which we were awarded in September 2006 as part of the NIH's Knockout Mouse Project.

Contract manufacturing revenue for the third quarter of 2006 related to our long-term agreement with Merck & Co., Inc., which expired in October 2006, to manufacture a vaccine intermediate at our Rensselaer, New York facility. Revenue and the related manufacturing

expense were recognized as product was shipped, after acceptance by Merck. Included in contract manufacturing revenue in the third quarter of 2006 was $0.4 million of deferred revenue associated with capital improvement reimbursements paid by Merck prior to commencement of production. We do not expect to receive any further contract manufacturing revenue from Merck.

In connection with our license agreement with AstraZeneca, as described above, the $20.0 million non-refundable up-front payment, which we received in February 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. In connection with our license agreement with Astellas, as described above, the $20.0 million non-refundable up-front payment, which we received in April 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. In the third quarter of 2007, we recognized $10.0 million of technology licensing revenue related to these agreements.

Expenses:

Total operating expenses increased to $61.0 million in the third quarter of 2007 from $43.9 million in the same period of 2006. Our average employee headcount in the third quarter of 2007 increased to 639 from 557 in the third quarter of 2006, primarily to support our expanded development programs for the VEGF Trap-Eye and rilonacept, and our plans to move our first antibody candidate into clinical trials. Operating expenses in the third quarter of 2007 and 2006 include a total of $7.0 million and $4.7 million, respectively, of non-cash compensation expense related to employee stock option awards (Stock Option Expense), as detailed below:

	For the three months ended September 30, 2007		
(In millions) **Expenses**	**Expenses before inclusion of Stock Option Expense**	**Stock Option Expense**	**Expenses as Reported**
Research and development	$ 47.6	$ 4.1	$ 51.7
General and administrative	6.4	2.9	9.3
Total operating expenses	$ 54.0	$ 7.0	$ 61.0

	For the three months ended September 30, 2006		
(In millions) **Expenses**	**Expenses before inclusion of Stock Option Expense**	**Stock Option Expense**	**Expenses as Reported**
Research and development	$ 32.1	$ 2.7	$ 34.8
Contract manufacturing	3.0	0.1	3.1
General and administrative	4.1	1.9	6.0
Total operating expenses	$ 39.2	$ 4.7	$ 43.9

The increase in total Stock Option Expense in the third quarter of 2007 was primarily due to the higher fair market value of our Common Stock on the date of our annual employee option grants made in December 2006 in comparison to the fair market value of our Common Stock on the dates of annual employee option grants made in recent prior years.

Research and Development Expenses:

Research and development expenses increased to $51.7 million in the third quarter of 2007 from $34.8 million in the same period of 2006. The following table summarizes the major

categories of our research and development expenses for the three months ended September 30, 2007 and 2006:

(In millions) Research and development expenses	Three months ended September 30, 2007	2006	Increase
Payroll and benefits (1)	$ 15.2	$ 11.0	$ 4.2
Clinical trial expenses	12.9	3.1	9.8
Clinical manufacturing costs (2)	11.9	10.0	1.9
Research and preclinical development costs	5.8	5.5	0.3
Occupancy and other operating costs	5.9	5.2	0.7
Total research and development	$ 51.7	$ 34.8	$ 16.9

(1) Includes $3.4 million and $2.3 million of Stock Option Expense for the three months ended September 30, 2007 and 2006, respectively.

(2) Represents the full cost of manufacturing drug for use in research, preclinical development, and clinical trials, including related payroll and benefits, Stock Option Expense, manufacturing materials and supplies, depreciation, and occupancy costs of our Rensselaer manufacturing facility. Includes $0.7 million and $0.5 million of Stock Option Expense for the three months ended September 30, 2007 and 2006, respectively.

Payroll and benefits increased primarily due to higher compensation expense due, in part, to the increase in employee headcount, as described above and annual salary increases effective January 1, 2007, and higher Stock Option Expense, as described above. Clinical trial expenses increased due primarily to (i) higher costs related to our ongoing Phase 1 and 2 studies of the VEGF Trap-Eye in wet AMD, (ii) costs related to our Phase 3 study of the VEGF Trap-Eye in wet AMD, which we initiated in the third quarter of 2007, and (iii) higher rilonacept costs. Clinical manufacturing costs increased primarily due to higher costs related to manufacturing rilonacept and preclinical and clinical supplies of our first antibody drug candidate. Research and preclinical development costs increased primarily due to higher costs related to our human monoclonal antibody programs and utilization of our proprietary technology platforms, such as for our NIH grant, as described above. Occupancy and other operating costs increased primarily as a result of higher facility-related and maintenance costs.

We budget our research and development costs by expense category, rather than by project. We also prepare estimates of research and development costs for projects in clinical development, which include direct costs and allocations of certain costs such as indirect labor, non-cash stock-based employee compensation expense related to stock option awards, and manufacturing and other costs related to activities that benefit multiple projects. Our estimates of research and development costs for clinical development programs are shown below:

(In millions) Project Costs	Three months ended September 30, 2007	2006	Increase (Decrease)
Rilonacept	$ 12.9	$ 7.7	$ 5.2
Aflibercept (VEGF Trap) – Oncology	5.5	5.5	
VEGF Trap- Eye	14.1	5.8	8.3
Other research programs & unallocated costs	19.2	15.8	3.4
Total research and development expenses	$ 51.7	$ 34.8	$ 16.9

Drug development and approval in the United States is a multi-step process regulated by the FDA. The process begins with discovery and preclinical evaluation, leading up to the submission of an IND to the FDA which, if successful, allows the opportunity for study in

humans, or clinical study, of the potential new drug. Clinical development typically involves three phases of study: Phase 1, 2 and 3. The most significant costs in clinical development are in Phase 3 clinical trials, as they tend to be the longest and largest studies in the drug development process. Following successful completion of Phase 3 clinical trials for a biological product, a biologics license application (or BLA) must be submitted to, and accepted by, the FDA, and the FDA must approve the BLA prior to commercialization of the drug. It is not uncommon for the FDA to request additional data following its review of a BLA, which can significantly increase the drug development timeline and expenses. We may elect either on our own, or at the request of the FDA, to conduct further studies that are referred to as Phase 3B and 4 studies. Phase 3B studies are initiated and either completed or substantially completed while the BLA is under FDA review. These studies are conducted under an IND. Phase 4 studies, also referred to as post-marketing studies, are studies that are initiated and conducted after the FDA has approved a product for marketing. In addition, as discovery research, preclinical development, and clinical programs progress, opportunities to expand development of drug candidates into new disease indications can emerge. We may elect to add such new disease indications to our development efforts (with the approval of our collaborator for joint development programs), thereby extending the period in which we will be developing a product. For example, we, and our collaborators, where applicable, continue to explore further development of rilonacept, aflibercept, and the VEGF Trap-Eye in different disease indications.

There are numerous uncertainties associated with drug development, including uncertainties related to safety and efficacy data from each phase of drug development, uncertainties related to the enrollment and performance of clinical trials, changes in regulatory requirements, changes in the competitive landscape affecting a product candidate, and other risks and uncertainties described below in Item 1A, "Risk Factors" under "Risks Related to Development of Our Product Candidates," "Regulatory and Litigation Risks," and "Risks Related to Commercialization of Products." The lengthy process of seeking FDA approvals, and subsequent compliance with applicable statutes and regulations, require the expenditure of substantial resources. Any failure by us to obtain, or delay in obtaining, regulatory approvals could materially adversely affect our business.

For these reasons and due to the variability in the costs necessary to develop a product and the uncertainties related to future indications to be studied, the estimated cost and scope of the projects, and our ultimate ability to obtain governmental approval for commercialization, accurate and meaningful estimates of the total cost to bring our product candidates to market are not available. Similarly, we are currently unable to reasonably estimate if our product candidates will generate product revenues and material net cash inflows. In the second quarter of 2007, we submitted a BLA for our rilonacept for the treatment of CAPS, a group of rare genetic disorders. We cannot predict whether or when the commercialization of rilonacept in CAPS will result in a material net cash inflow to us.

Contract Manufacturing Expenses:

Contract manufacturing expenses decreased in the third quarter of 2007 compared to the same period of 2006 due to the expiration of our manufacturing agreement with Merck in October 2006.

General and Administrative Expenses:

General and administrative expenses increased to $9.3 million in the third quarter of 2007 from $6.0 million in the same period of 2006 primarily due to (i) higher Stock Option Expense, as described above, (ii) higher compensation expense due, in part, to increases in administrative headcount in 2007 to support our expanded research and development activities and annual salary increases effective January 1, 2007, (iii) higher recruitment and related costs associated with expanding our headcount in 2007, (iv) higher fees for consultants and other professional services on various corporate matters, (v) marketing research and related expenses incurred in 2007 in connection with our rilonacept and VEGF Trap-Eye programs, and (vi) higher administrative facility and occupancy costs.

Other Income and Expense:

Investment income increased to $5.8 million in the third quarter of 2007 from $3.9 million in the same period of 2006 resulting primarily from higher balances of cash and marketable securities (due, in part, to the up-front payment received from Bayer HealthCare in October 2006, as described above, and the receipt of net proceeds from the November 2006 public offering of our Common Stock). This increase was partly offset by a $0.8 million charge in the third quarter of 2007 related to marketable securities which we considered to be other than temporarily impaired. Interest expense was $3.0 million in the third quarter of 2007 and 2006. Interest expense is attributable primarily to $200.0 million of convertible notes issued in October 2001, which mature in October 2008 and bear interest at 5.5% per annum.

Nine Months Ended September 30, 2007 and 2006

Net Loss:

Regeneron reported a net loss of $92.5 million, or $1.40 per share (basic and diluted), for the first nine months of 2007 compared to a net loss of $71.4 million, or $1.25 per share (basic and diluted), for the same period of 2006.

Revenues:

Revenues for the nine months ended September 30, 2007 and 2006 consist of the following:

(In millions)	2007	2006	Increase (Decrease)
Contract research & development revenue			
The sanofi-aventis Group	$ 34.5	$ 38.7	$ (4.2)
Other	7.4	2.3	5.1
Total contract research & development revenue	41.9	41.0	0.9
Contract manufacturing revenue		12.1	(12.1)
Technology licensing revenue	18.4		18.4
Total revenue	$ 60.3	$ 53.1	$ 7.2

We recognize revenue from sanofi-aventis, in connection with the companies' aflibercept collaboration, in accordance with SAB 104 and EITF 00-21. We earn contract research and development revenue from sanofi-aventis which, as detailed below, consists partly of reimbursement for research and development expenses and partly of the recognition of revenue

related to a total of $105.0 million of non-refundable, up-front payments received in 2003 and 2006. Non-refundable up-front license payments are recorded as deferred revenue and recognized over the period over which we are obligated to perform services. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances.

Sanofi-aventis Contract Research & Development Revenue *(In millions)*	**Nine months ended September 30, 2007**	**2006**
Regeneron expense reimbursement	$ 27.8	$ 29.6
Recognition of deferred revenue related to up-front payments	6.7	9.1
Total	$ 34.5	$ 38.7

Sanofi-aventis' reimbursement of Regeneron aflibercept expenses decreased in the first nine months of 2007 from the same period in 2006, primarily due to higher costs in 2006 related to the Company's manufacture of aflibercept clinical supplies. Recognition of deferred revenue related to sanofi-aventis' up-front payments decreased for the first nine months of 2007 from the same period in 2006, due to an extension of the estimated performance period over which this deferred revenue is being recognized. As of September 30, 2007, $63.2 million of the original $105.0 million of up-front payments was deferred and will be recognized as revenue in future periods.

Other contract research and development revenue includes $4.5 million and $0.1 million for the first nine months of 2007 and 2006, respectively, recognized in connection with our five-year grant from the NIH, which we were awarded in September 2006 as part of the NIH's Knockout Mouse Project.

Contract manufacturing revenue for the first nine months of 2006 related to our long-term manufacturing agreement with Merck, which expired in October 2006. Revenue and the related manufacturing expense were recognized as product was shipped, after acceptance by Merck. Included in contract manufacturing revenue in the third quarter of 2006 was $1.2 million of deferred revenue associated with capital improvement reimbursements paid by Merck prior to commencement of production. We do not expect to receive any further contract manufacturing revenue from Merck.

In connection with our license agreement with AstraZeneca, as described above, the $20.0 million non-refundable up-front payment, which we received in February 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in February 2007. In connection with our license agreement with Astellas, as described above, the $20.0 million non-refundable up-front payment, which we received in April 2007, was deferred and is being recognized as revenue ratably over the twelve month period beginning in June 2007. In the first nine months of 2007, we recognized $18.4 million of technology licensing revenue related to these agreements.

Expenses:

Total operating expenses increased to $163.2 million in the first nine months of 2007 from $127.3 million in the same period of 2006. Our average employee headcount in the first nine months of 2007 increased to 614 from 574 in the first nine months of 2006, primarily to support our expanded development programs for the VEGF Trap-Eye and rilonacept and our plans to

move our first antibody candidate into clinical trials. Operating expenses for the first nine months of 2007 and 2006 include a total of $20.5 million and $13.2 million, respectively, of Stock Option Expense, as detailed below:

	For the nine months ended September 30, 2007		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 124.8	$ 12.0	$ 136.8
General and administrative	17.9	8.5	26.4
Total operating expenses	$ 142.7	$ 20.5	$ 163.2

	For the nine months ended September 30, 2006		
(In millions) Expenses	Expenses before inclusion of Stock Option Expense	Stock Option Expense	Expenses as Reported
Research and development	$ 94.0	$ 7.3	$ 101.3
Contract manufacturing	7.4	0.3	7.7
General and administrative	12.7	5.6	18.3
Total operating expenses	$ 114.1	$ 13.2	$ 127.3

The increase in total Stock Option Expense in the first nine months of 2007 was primarily due to the higher fair market value of our Common Stock on the date of our annual employee option grants made in December 2006 in comparison to the fair market value of our Common Stock on the dates of annual employee option grants made in recent prior years.

Research and Development Expenses:

Research and development expenses increased to $136.8 million in the first nine months of 2007 from $101.3 million in the same period of 2006. The following table summarizes the major categories of our research and development expenses for the nine months ended September 30, 2007 and 2006:

	Nine months ended September 30,		
(In millions) Research and development expenses	2007	2006	Increase
Payroll and benefits (1)	$ 43.3	$ 32.7	$ 10.6
Clinical trial expenses	24.8	11.0	13.8
Clinical manufacturing costs (2)	33.8	28.3	5.5
Research and preclinical development costs	17.9	13.3	4.6
Occupancy and other operating costs	17.0	16.0	1.0
Total research and development	$ 136.8	$ 101.3	$ 35.5

(1) Includes $9.8 million and $6.1 million of Stock Option Expense for the nine months ended September 30, 2007 and 2006, respectively.

(2) Represents the full cost of manufacturing drug for use in research, preclinical development, and clinical trials, including related payroll and benefits, Stock Option Expense, manufacturing materials and supplies, depreciation, and occupancy costs of our Rensselaer manufacturing facility. Includes $2.2 million and $1.2 million of Stock Option Expense for the nine months ended September 30, 2007 and 2006, respectively.

Payroll and benefits increased primarily due to higher compensation expense due, in part, to the increase in employee headcount, as described above and annual salary increases effective January 1, 2007, and higher Stock Option Expense, as described above. Clinical trial expenses

increased due primarily to (i) higher costs related to our ongoing Phase 1 and 2 studies of the VEGF Trap-Eye in wet AMD, (ii) costs related to our Phase 3 study of the VEGF Trap-Eye in wet AMD, which we initiated in the third quarter of 2007, and (iii) higher rilonacept costs. Clinical manufacturing costs increased due primarily to higher costs related to manufacturing rilonacept and preclinical and clinical supplies of our first antibody drug candidate, which were partly offset by lower costs related to manufacturing VEGF Trap. Research and preclinical development costs increased primarily due to higher costs related to our human monoclonal antibody programs and utilization of our proprietary technology platforms, such as for our NIH grant, as described above. Occupancy and other operating costs increased primarily as a result of higher facility-related and maintenance costs.

We budget our research and development costs by expense category, rather than by project. We also prepare estimates of research and development cost for projects in clinical development, which include direct costs and allocations of certain costs such as indirect labor, non-cash stock-based employee compensation expense related to stock option awards, and manufacturing and other costs related to activities that benefit multiple projects. Our estimates of research and development costs for clinical development programs are shown below:

(In millions)	Nine months ended September 30,		
Project Costs	**2007**	**2006**	**Increase (Decrease)**
Rilonacept	$ 28.7	$ 22.0	$ 6.7
Aflibercept (VEGF Trap) – Oncology	23.3	24.8	(1.5)
VEGF Trap- Eye	28.3	13.7	14.6
Other research programs & unallocated costs	56.5	40.8	15.7
Total research and development expenses	$ 136.8	$ 101.3	$ 35.5

For the reasons described above under "Research and Development Expenses" for the three months ended September 30, 2007 and 2006, and due to the variability in the costs necessary to develop a product and the uncertainties related to future indications to be studied, the estimated cost and scope of the projects, and our ultimate ability to obtain governmental approval for commercialization, accurate and meaningful estimates of the total cost to bring our product candidates to market are not available. Similarly, we are currently unable to reasonably estimate if our product candidates will generate product revenues and material net cash inflows.

Contract Manufacturing Expenses:

Contract manufacturing expenses decreased in the first nine months of 2007 compared to the same period of 2006 due to the expiration of our manufacturing agreement with Merck in October 2006.

General and Administrative Expenses:

General and administrative expenses increased to $26.4 million in the first nine months of 2007 from $18.3 million in the same period of 2006 primarily due to (i) higher Stock Option Expense, as described above, (ii) higher compensation expense due, in part, to increases in administrative headcount in 2007 to support our expanded research and development activities and annual salary increases effective January 1, 2007, (iii) higher recruitment and related costs

associated with expanding our headcount in 2007, (iv) higher fees for consultants and other professional services on various corporate matters, and (v) marketing research and related expenses incurred in 2007 in connection with our rilonacept and VEGF Trap-Eye programs.

Other Income and Expense:

Investment income increased to $19.4 million in the first nine months of 2007 from $11.0 million in the same period of 2006 resulting primarily from higher balances of cash and marketable securities (due, in part, to the up-front payment received from Bayer HealthCare in October 2006, as described above, and the receipt of net proceeds from the November 2006 public offering of our Common Stock). This increase was partly offset by a $0.8 million charge in the first nine months of 2007 related to marketable securities which, during the third quarter of 2007, we considered to be other than temporarily impaired. Interest expense was $9.0 million in first nine months of 2007 and 2006. Interest expense is attributable primarily to $200.0 million of convertible notes issued in October 2001, which mature in October 2008 and bear interest at 5.5% per annum.

Liquidity and Capital Resources

Since our inception in 1988, we have financed our operations primarily through offerings of our equity securities, a private placement of convertible debt, payments earned under our past and present research and development and contract manufacturing agreements, including our agreements with sanofi-aventis, Bayer HealthCare, and Merck, and investment income.

Nine Months Ended September 30, 2007 and 2006

At September 30, 2007, we had $497.3 million in cash, cash equivalents, restricted cash, and marketable securities, compared with $522.9 million at December 31, 2006. In connection with our new non-exclusive license agreements with AstraZeneca and Astellas, as described above, AstraZeneca and Astellas each made an up-front payment to us of $20.0 million in February and April 2007, respectively. In the third quarter of 2007, the Company received a $20.0 million milestone payment from Bayer HealthCare following dosing of the first patient in the Phase 3 study of the VEGF Trap-Eye in wet AMD.

Cash Used in Operations:

Net cash used in operations was $23.4 million in the first nine months of 2007, compared to $30.2 million in the first nine months of 2006. Our net losses of $92.5 million in the first nine months of 2007 and $71.4 million in the first nine months of 2006 included $20.5 million and $13.5 million, respectively, of non-cash stock-based employee compensation costs, of which $20.5 million and $13.2 million, respectively, represented Stock Option Expense and, in the first nine months of 2006, $0.3 million represented non-cash compensation expense from Restricted Stock awards. At September 30, 2007, our deferred revenue balances increased by $46.8 million, compared to year end 2006, due, in part, to the unrecognized balances of the two $20.0 million up-front payments received from each of AstraZeneca and Astellas, as described above. In addition, for the first nine months of 2007, the $20.0 million development milestone payment received from Bayer HealthCare in August 2007 and reimbursements from Bayer HealthCare of our 2007 VEGF Trap-Eye development expenses, totaling $12.9 million, have been fully

deferred and included in deferred revenue for financial statement purposes, as discussed above. At September 30, 2006, accounts receivable balances decreased by $28.6 million, compared to year end 2005, primarily due to the January 2006 receipt of a $25.0 million up-front payment from sanofi-aventis, which was receivable at December 31, 2005, in connection with an amendment to our collaboration agreement to include Japan. Also, our deferred revenue balances at September 30, 2006 decreased by $12.5 million, compared to year end 2005, due primarily to the revenue recognition of $9.1 million of deferred revenue related to up-front payments from sanofi-aventis during the first nine months of 2006. The majority of our cash expenditures in both the first nine months of 2007 and 2006 were to fund research and development, primarily related to our clinical programs and, in the first nine months of 2007, our preclinical human monoclonal antibody programs.

Cash (Used in) Provided by Investing Activities:

Net cash used in investing activities was $122.2 million in the first nine months of 2007 compared to net cash provided by investing activities of $8.1 million in the same period of 2006, due primarily to an increase in purchases of marketable securities net of sales or maturities. In the first nine months of 2007, purchases of marketable securities exceeded sales or maturities by $114.5 million, whereas in the first nine months of 2006, sales or maturies of marketable securities exceeded purchases by $9.7 million.

Cash Provided by Financing Activities:

Cash provided by financing activities, which in the first nine months of 2007 and 2006 is attributable primarily to the issuance of Common Stock in connection with exercises of employee stock options, decreased slightly to $5.2 million in the first nine months of 2007 from $5.3 million in the same period in 2006.

License Agreements with AstraZeneca and Astellas:

Under these non-exclusive license agreements, AstraZeneca and Astellas each made a $20.0 million non-refundable, up-front payment to us in February and April 2007, respectively. AstraZeneca and Astellas also will each make up to five additional annual payments of $20.0 million, subject to each licensee's ability to terminate its license agreement with us after making the first three additional payments or earlier if the technology does not meet minimum performance criteria.

Capital Expenditures:

Our additions to property, plant, and equipment totaled $7.9 million and $1.8 million for the first nine months of 2007 and 2006, respectively. During the remainder of 2007, we expect to incur approximately $10-12 million in capital expenditures (including approximately $9 million to purchase a facility in Rensselaer, New York, as described below) primarily to support our manufacturing, development, and research activities.

During the second quarter of 2007, we exercised a purchase option on a building in Rensselaer, totaling approximately 270,000 square feet, in which we leased approximately 75,000 square feet of manufacturing, office and warehouse space. We completed the purchase of

this property (land and building) in October 2007 at a cost of approximately $9 million, which is included in our anticipated capital expenditures for the remainder of 2007, as described above. The space that we do not occupy in this building is currently leased to another tenant.

Convertible Debt:

In 2001, we issued $200.0 million aggregate principal amount of convertible senior subordinated notes, which bear interest at 5.5% per annum, payable semi-annually, and mature in October 2008. The notes are convertible into shares of our Common Stock at a conversion price of approximately $30.25 per share, subject to adjustment in certain circumstances. If the price per share of our Common Stock is above $30.25 at maturity, we would expect the notes to convert into shares of Common Stock. Otherwise, we will be required to repay the $200.0 million aggregate principal amount of the notes or refinance the notes prior to maturity; however, we can provide no assurance that we will be able to successfully arrange such refinancing.

Amendment to Operating Lease – Tarrytown, New York Facilities:

We currently lease approximately 232,000 square feet of laboratory and office facilities in Tarrytown, New York. In December 2006, we entered into a new lease agreement to lease approximately 221,000 square feet of laboratory and office space at our current Tarrytown location, which includes approximately 27,000 square feet that would be retained from our current space and approximately 194,000 square feet in new facilities that are currently under construction and expected to be completed in mid-2009. In October 2007, we amended the December 2006 operating lease agreement to increase the amount of new space we will lease from approximately 194,000 square feet to approximately 230,000 square feet, for an amended total under the new lease of 257,000 square feet. The term of the lease is now expected to commence in mid-2008 and will expire approximately 16 years later. Other terms and conditions, as previously described in our Form 10-K for the year ended December 31, 2006, remain unchanged.

Funding Requirements:

We expect to continue to incur substantial funding requirements primarily for research and development activities (including preclinical and clinical testing). Before taking into account reimbursements from collaborators, we currently anticipate that approximately 55-65% of our expenditures for 2007 will be directed toward the preclinical and clinical development of product candidates, including rilonacept, aflibercept, VEGF Trap-Eye and monoclonal antibodies; approximately 10-15% of our expenditures for 2007 will be applied to our basic research activities and the continued development of our novel technology platforms; and the remainder of our expenditures for 2007 will be used for capital expenditures and general corporate purposes.

In connection with the amendment to our new operating lease agreement on our Tarrytown facilities and the purchase of a building in Rensselaer where we leased manufacturing, warehouse and office space, each as described above, our previously disclosed funding requirements for operating leases, as per our Form 10-K for the year ended December 31, 2006, will decrease for the two-year period beginning January 1, 2008 from $15.6 million to $13.9

million, increase for the two-year period beginning January 1, 2010 from $24.0 million to $28.6 million, and increase, in the aggregate, for fiscal years beginning January 1, 2012 and thereafter from $161.4 million to $204.2 million.

Under our collaboration with Bayer HealthCare, over the next several years we and Bayer HealthCare are sharing agreed upon VEGF Trap-Eye development expenses incurred by both companies, under a global development plan, as follows:

2007: Up to $50.0 million shared equally; we are solely responsible for up to the next $40.0 million; over $90.0 million shared equally. Through September 30, 2007, cumulative shared development expenses have exceeded $50.0 million.

2008: Up to $70.0 million shared equally, we are solely responsible for up to the next $30.0 million; over $100.0 million shared equally.

2009 and thereafter: All expenses shared equally.

In addition, under our collaboration agreements with sanofi-aventis and Bayer Healthcare, if the applicable collaboration becomes profitable, we have contingent contractual obligations to reimburse sanofi-aventis and Bayer Healthcare for 50% of agreed-upon development expenses incurred by sanofi-aventis and Bayer Healthcare, respectively. Profitability under each collaboration will be measured by calculating net sales less agreed-upon expenses. These reimbursements would be deducted from our share of the collaboration profits (and, for sanofi-aventis, royalties on product sales in Japan) otherwise payable to us unless we agree to reimburse these expenses at a faster rate at our option. Given the uncertainties related to drug development (including the development of the aflibercept in collaboration with sanofi-aventis and the VEGF Trap-Eye in collaboration with Bayer Healthcare) such as the variability in the length of time necessary to develop a product candidate and the ultimate ability to obtain governmental approval for commercialization, we are currently unable to reliably estimate if our collaborations with sanofi-aventis and Bayer Healthcare will become profitable.

The amount we need to fund operations will depend on various factors, including the status of competitive products, the success of our research and development programs, the potential future need to expand our professional and support staff and facilities, the status of patents and other intellectual property rights, the delay or failure of a clinical trial of any of our potential drug candidates, and the continuation, extent, and success of our collaborations with sanofi-aventis and Bayer HealthCare. Clinical trial costs are dependent, among other things, on the size and duration of trials, fees charged for services provided by clinical trial investigators and other third parties, the costs for manufacturing the product candidate for use in the trials, supplies, laboratory tests, and other expenses. The amount of funding that will be required for our clinical programs depends upon the results of our research and preclinical programs and early-stage clinical trials, regulatory requirements, the clinical trials underway plus additional clinical trials that we decide to initiate, and the various factors that affect the cost of each trial as described above. In the future, if we are able to successfully develop, market, and sell certain of our product candidates, we may be required to pay royalties or otherwise share the profits generated on such sales in connection with our collaboration and licensing agreements.

We expect that expenses related to the filing, prosecution, defense, and enforcement of patent and other intellectual property claims will continue to be substantial as a result of patent filings and prosecutions in the United States and foreign countries.

We believe that our existing capital resources will enable us to meet operating needs through at least early 2010, without taking into consideration the $200.0 million aggregate principal amount of convertible senior subordinated notes, which mature in October 2008. However, this is a forward-looking statement based on our current operating plan, and there may be a change in projected revenues or expenses that would lead to our capital being consumed significantly before such time. If there is insufficient capital to fund all of our planned operations and activities, we believe we would prioritize available capital to fund preclinical and clinical development of our product candidates. Other than a $1.6 million letter of credit issued to our landlord in connection with our new operating lease for facilities in Tarrytown, New York, we have no off-balance sheet arrangements. In addition, we do not guarantee the obligations of any other entity. As of September 30, 2007, we had no established banking arrangements through which we could obtain short-term financing or a line of credit. In the event we need additional financing for the operation of our business, we will consider collaborative arrangements and additional public or private financing, including additional equity financing. Factors influencing the availability of additional financing include our progress in product development, investor perception of our prospects, and the general condition of the financial markets. We may not be able to secure the necessary funding through new collaborative arrangements or additional public or private offerings. If we cannot raise adequate funds to satisfy our capital requirements, we may have to delay, scale back, or eliminate certain of our research and development activities or future operations. This could harm our business.

Critical Accounting Policies and Significant Judgments and Estimates

Revenue Recognition:

We recognize revenue from contract research and development and research progress payments in accordance with Staff Accounting Bulletin No. 104, *Revenue Recognition* (SAB 104) and Emerging Issues Task Force 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables* (EITF 00-21). We earn contract research and development revenue and research progress payments in connection with collaboration and other agreements to develop and commercialize product candidates and utilize our technology platforms. The terms of these agreements typically include non-refundable up-front licensing payments, research progress (milestone) payments, and payments for development activities. Non-refundable up-front license payments, where continuing involvement is required of us, are deferred and recognized over the related performance period. We estimate our performance period based on the specific terms of each agreement, and adjust the performance periods, if appropriate, based on the applicable facts and circumstances. Payments which are based on achieving a specific substantive performance milestone, involving a degree of risk, are recognized as revenue when the milestone is achieved and the related payment is due and non-refundable, provided there is no future service obligation associated with that milestone. Substantive performance milestones typically consist of significant achievements in the development life-cycle of the related product candidate, such as completion of clinical trials, filing for approval with regulatory agencies, and approvals by regulatory agencies. In determining whether a payment is deemed to be a substantive performance milestone, we take into consideration (i) the nature, timing, and value of significant achievements in the development life- cycle of the related development product candidate, (ii) the relative level of effort required to achieve the milestone, and (iii) the relative level of risk in achieving the milestone, taking into account the high degree of uncertainty in

successfully advancing product candidates in a drug development program and in ultimately attaining an approved drug product. Payments for achieving milestones which are not considered substantive are accounted for as license payments and recognized over the related performance period. Payments for development activities where Regeneron is not sharing costs are recognized as revenue as earned, over the period of effort. In addition, we record revenue in connection with a government research grant as we incur expenses related to the grant, subject to the grant's terms and annual funding approvals.

In connection with non-refundable licensing payments, our performance period estimates are principally based on projections of the scope, progress, and results of our research and development activities. Due to the variability in the scope of activities and length of time necessary to develop a drug product, changes to development plans as programs progress, and uncertainty in the ultimate requirements to obtain governmental approval for commercialization, revisions to performance period estimates are possible, and could result in material changes to the amount of revenue recognized each year in the future. In addition, performance periods may be extended if we and our collaborators decide to expand our clinical plans for a drug candidate into additional disease indications. Also, if a collaborator terminates an agreement in accordance with the terms of the agreement, we would recognize any unamortized remainder of an up-front payment at the time of the termination. For the year ended December 31, 2006, changes in estimates of our performance periods, including an extension of our estimated performance period for our collaboration with sanofi-aventis, did not have a material impact on contract research and development revenue that we recognized. In 2007, we currently expect to recognize at least $2.4 million lower contract research and development revenue, compared to amounts recognized in 2006, in connection with $105.0 million of non-refundable up-front payments previously received from sanofi-aventis, due to an extension of our estimated performance period.

As described above, we and Bayer HealthCare are currently formalizing our global development plans for the VEGF Trap-Eye in wet AMD and DME. Pending completion of these plans, all payments received or receivable from Bayer HealthCare through September 30, 2007 have been fully deferred and included in deferred revenue for financial statement purposes. When the plans are formalized later this year, we will determine the appropriate accounting policy for payments from Bayer HealthCare and the financial statement classifications and periods in which past and future payments from Bayer (including the $75.0 million up-front payment, development and regulatory milestone payments, and reimbursements of Regeneron development expenses) will be recognized in our Statement of Operations. In the period when we commence recognizing previously deferred payments from Bayer HealthCare, we anticipate recording a cumulative catch-up for the period since inception of the collaboration in October 2006, which cannot be quantified at this time.

Clinical Trial Expenses:

Clinical trial costs are a significant component of research and development expenses and include costs associated with third-party contractors. We outsource a substantial portion of our clinical trial activities, utilizing external entities such as contract research organizations, independent clinical investigators, and other third-party service providers to assist us with the execution of our clinical studies. For each clinical trial that we conduct, certain clinical trial costs are expensed immediately, while others are expensed over time based on the expected total number of patients in the trial, the rate at which patients enter the trial, and the period over which clinical investigators or contract research organizations are expected to provide services.

Clinical activities which relate principally to clinical sites and other administrative functions to manage our clinical trials are performed primarily by contract research organizations (CROs). CROs typically perform most of the start-up activities for our trials, including document preparation, site identification, screening and preparation, pre-study visits, training, and program management. On a budgeted basis, these start-up costs are typically 10% to 15% of the total contract value. On an actual basis, this percentage range can be significantly wider, as many of our contracts are either expanded or reduced in scope compared to the original budget, while start-up costs for the particular trial may not change materially. These start-up costs usually occur within a few months after the contract has been executed and are event driven in nature. The remaining activities and related costs, such as patient monitoring and administration, generally occur ratably throughout the life of the individual contract or study. In the event of early termination of a clinical trial, we accrue and recognize expenses in an amount based on our estimate of the remaining non-cancelable obligations associated with the winding down of the clinical trial and/or penalties.

For clinical study sites, where payments are made periodically on a per-patient basis to the institutions performing the clinical study, we accrue on an estimated cost-per-patient basis an expense based on subject enrollment and activity in each quarter. The amount of clinical study expense recognized in a quarter may vary from period to period based on the duration and progress of the study, the activities to be performed by the sites each quarter, the required level of patient enrollment, the rate at which patients actually enroll in and drop-out of the clinical study, and the number of sites involved in the study. Clinical trials that bear the greatest risk of change in estimates are typically those with a significant number of sites, require a large number of patients, have complex patient screening requirements, and span multiple years. During the course of a trial, we adjust our rate of clinical expense recognition if actual results differ from our estimates. Our estimates and assumptions for clinical expense recognition could differ significantly from our actual results, which could cause material increases or decreases in research and development expenses in future periods when the actual results become known. No material adjustments to our past clinical trial accrual estimates were made during the year ended December 31, 2006 or the nine months ended September 30, 2007.

During the three months ended September 30, 2007, there were no changes to any other "Critical Accounting Policies and Significant Judgments and Estimates" described in our Annual Report on Form 10-K for the year ended December 31, 2006.

Future Impact of Recently Issued Accounting Standards

In February 2007, the Financial Accounting Standards Board (FASB) issued Statement of Financial Accounting Standards No. (SFAS) 159, *The Fair Value Option for Financial Assets and Financial Liabilities* . SFAS 159 permits entities to choose to measure many financial instruments and certain other items at fair value. The objective is to improve financial reporting by providing entities with the opportunity to mitigate volatility in reported earnings caused by measuring related assets and liabilities differently without having to apply complex hedge accounting provisions. SFAS 159 is effective for financial statements issued for fiscal years beginning after November 15, 2007. We will be required to adopt SFAS 159 effective for the fiscal year beginning January 1, 2008. Our management is currently evaluating the potential impact of adopting SFAS 159 on our financial statements.

In June 2007, the Emerging Issues Task Force issued Statement No. 07-3, *Accounting for Non-refundable Advance Payments for Goods or Services to Be Used in Future Research and Development Activities* (EITF 07-3). EITF 07-3 addresses how entities involved in research and development activities should account for the non-refundable portion of an advance payment made for future research and development activities and requires that such payments be deferred and capitalized, and recognized as an expense when the goods are delivered or the related services are performed. EITF 07-3 is effective for fiscal years beginning after December 15, 2007, including interim periods within those fiscal years. We will be required to adopt EITF 07-3 effective for the fiscal year beginning January 1, 2008. Our management believes that the future adoption of EITF 07-3 will not have a material impact on our financial statements.

Item 3. Quantitative and Qualitative Disclosure About Market Risk

Interest Rate Risk:

Our earnings and cash flows are subject to fluctuations due to changes in interest rates primarily from our investment of available cash balances in investment grade corporate, asset-backed, and U.S. government securities. We do not believe we are materially exposed to changes in interest rates. Under our current policies we do not use interest rate derivative instruments to manage exposure to interest rate changes. We estimate that a one percent unfavorable change in interest rates would result in approximately a $2.2 million and $0.5 million decrease in the fair market value of our investment portfolio at September 30, 2007 and 2006, respectively. The increase in the potential impact of an interest rate change at September 30, 2007, compared to September 30, 2006, is due primarily to increases in our investment portfolio's balance and duration at the end of September 2007 versus September 2006.

Credit Quality Risk:

We have an investment policy that includes guidelines on acceptable investment securities, minimum credit quality, maturity parameters, and concentration and diversification. Nonetheless, deterioration of the credit quality of an investment security subsequent to purchase may subject us to the risk of not being able to recover the full principal value of the security. In the third quarter of 2007, we recognized a $0.8 million charge related to securities that we considered to be other than temporarily impaired.

Item 4. Controls and Procedures

Our management, with the participation of our chief executive officer and chief financial officer, conducted an evaluation of the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 (the "Exchange Act")), as of the end of the period covered by this report. Based on this evaluation, our chief executive officer and chief financial officer each concluded that, as of the end of such period, our disclosure controls and procedures were effective in ensuring that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in applicable rules and forms of the Securities and Exchange Commission, and is accumulated and communicated to our management, including our chief executive officer and chief financial officer, as appropriate to allow timely decisions regarding required disclosure.

There has been no change in our internal control over financial reporting (as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended September 30, 2007 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

Item 1. Legal Proceedings

From time to time, we are a party to legal proceedings in the course of our business. We do not expect any such current legal proceedings to have a material adverse effect on our business or financial condition.

Item 1A. Risk Factors

We operate in an environment that involves a number of significant risks and uncertainties. We caution you to read the following risk factors, which have affected, and/or in the future could affect, our business, operating results, financial condition, and cash flows. The risks described below include forward-looking statements, and actual events and our actual results may differ substantially from those discussed in these forward-looking statements. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also impair our business operations. Furthermore, additional risks and uncertainties are described under other captions in this report and in our Annual Report on Form 10-K for the year ended December 31, 2006 and should be considered by our investors.

Risks Related to Our Financial Results and Need for Additional Financing

We have had a history of operating losses and we may never achieve profitability. If we continue to incur operating losses, we may be unable to continue our operations.

From inception on January 8, 1988 through September 30, 2007, we had a cumulative loss of $780.1 million. If we continue to incur operating losses and fail to become a profitable company, we may be unable to continue our operations. We have no products that are available for sale and

do not know when we will have products available for sale, if ever. In the absence of revenue from the sale of products or other sources, the amount, timing, nature or source of which cannot be predicted, our losses will continue as we conduct our research and development activities.

We will need additional funding in the future, which may not be available to us, and which may force us to delay, reduce or eliminate our product development programs or commercialization efforts.

We will need to expend substantial resources for research and development, including costs associated with clinical testing of our product candidates. We believe our existing capital resources will enable us to meet operating needs through at least early 2010, without taking into consideration the $200.0 million aggregate principal amount of convertible senior subordinated notes, which mature in October 2008; however, our projected revenue may decrease or our expenses may increase and that would lead to our capital being consumed significantly before such time. We will likely require additional financing in the future and we may not be able to raise such additional funds. If we are able to obtain additional financing through the sale of equity or convertible debt securities, such sales may be dilutive to our shareholders. Debt financing arrangements may require us to pledge certain assets or enter into covenants that would restrict our business activities or our ability to incur further indebtedness and may contain other terms that are not favorable to our shareholders. If we are unable to raise sufficient funds to complete the development of our product candidates, we may face delay, reduction or elimination of our research and development programs or preclinical or clinical trials, in which case our business, financial condition or results of operations may be materially harmed.

We have a significant amount of debt and may have insufficient cash to satisfy our debt service and repayment obligations. In addition, the amount of our debt could impede our operations and flexibility.

We have a significant amount of convertible debt and semi-annual interest payment obligations. This debt, unless converted to shares of our common stock, will mature in October 2008. We may be unable to generate sufficient cash flow or otherwise obtain funds necessary to make required payments on our debt. Even if we are able to meet our debt service obligations, the amount of debt we already have could hurt our ability to obtain any necessary financing in the future for working capital, capital expenditures, debt service requirements, or other purposes. In addition, our debt obligations could require us to use a substantial portion of cash to pay principal and interest on our debt, instead of applying those funds to other purposes, such as research and development, working capital, and capital expenditures.

Risks Related to Development of Our Product Candidates

Successful development of any of our product candidates is highly uncertain.

Only a small minority of all research and development programs ultimately result in commercially successful drugs. We have never developed a drug that has been approved for marketing and sale, and we may never succeed in developing an approved drug. Even if clinical trials demonstrate safety and effectiveness of any of our product candidates for a specific disease and the necessary regulatory approvals are obtained, the commercial success of any of our product candidates will depend upon their acceptance by patients, the medical community, and

third-party payers and on our partners' ability to successfully manufacture and commercialize our product candidates. Our product candidates are delivered either by intravenous infusion or by intravitreal or subcutaneous injections, which are generally less well received by patients than tablet or capsule delivery. If our products are not successfully commercialized, we will not be able to recover the significant investment we have made in developing such products and our business would be severely harmed.

We are studying our lead product candidates, aflibercept, VEGF Trap-Eye, and rilonacept, in a wide variety of indications. We are studying aflibercept in a variety of cancer settings, the VEGF Trap-Eye in different eye diseases and ophthalmologic indications, and rilonacept in a variety of systemic inflammatory disorders. Many of these current trials are exploratory studies designed to identify what diseases and uses, if any, are best suited for our product candidates. It is likely that our product candidates will not demonstrate the requisite efficacy and/or safety profile to support continued development for most of the indications that are to be studied. In fact, our product candidates may not demonstrate the requisite efficacy and safety profile to support the continued development for any of the indications or uses.

Clinical trials required for our product candidates are expensive and time-consuming, and their outcome is highly uncertain. If any of our drug trials are delayed or achieve unfavorable results, we will have to delay or may be unable to obtain regulatory approval for our product candidates.

We must conduct extensive testing of our product candidates before we can obtain regulatory approval to market and sell them. We need to conduct both preclinical animal testing and human clinical trials. Conducting these trials is a lengthy, time-consuming, and expensive process. These tests and trials may not achieve favorable results for many reasons, including, among others, failure of the product candidate to demonstrate safety or efficacy, the development of serious or life-threatening adverse events (or side effects) caused by or connected with exposure to the product candidate, difficulty in enrolling and maintaining subjects in the clinical trial, lack of sufficient supplies of the product candidate or comparator drug, and the failure of clinical investigators, trial monitors and other consultants, or trial subjects to comply with the trial plan or protocol. A clinical trial may fail because it did not include a sufficient number of patients to detect the endpoint being measured or reach statistical significance. A clinical trial may also fail because the dose(s) of the investigational drug included in the trial were either too low or too high to determine the optimal effect of the investigational drug in the disease setting. For example, we are studying higher doses of rilonacept in different diseases after a Phase 2 trial using lower doses of rilonacept in subjects with rheumatoid arthritis failed to achieve its primary endpoint.

We will need to reevaluate any drug candidate that does not test favorably and either conduct new trials, which are expensive and time consuming, or abandon the drug development program. Even if we obtain positive results from preclinical or clinical trials, we may not achieve the same success in future trials. Many companies in the biopharmaceutical industry, including us, have suffered significant setbacks in clinical trials, even after promising results have been obtained in earlier trials. The failure of clinical trials to demonstrate safety and effectiveness for the desired indication(s) could harm the development of the product candidate(s), and our business, financial condition, and results of operations may be materially harmed.

The data from the Phase 3 clinical program for rilonacept in CAPS (Cryopyrin-Associated Periodic Syndromes) may be inadequate to support regulatory approval for commercialization of rilonacept.

We recently submitted a BLA to the FDA for rilonacept in CAPS. However, the efficacy and safety data from the Phase 3 clinical program included in the BLA may be inadequate to support approval for commercialization of rilonacept. The FDA and other regulatory agencies may have varying interpretations of our clinical trial data, which could delay, limit, or prevent regulatory approval or clearance.

Further, before a product candidate is approved for marketing, our manufacturing facilities must be inspected by the FDA and the FDA will not approve the product for marketing if we or our third party manufacturers are not in compliance with current good manufacturing practices. Even if the FDA and similar foreign regulatory authorities do grant marketing approval for rilonacept, they may pose restrictions on the use or marketing of the product, or may require us to conduct additional post-marketing trials. These restrictions and requirements would likely result in increased expenditures and lower revenues and may restrict our ability to commercialize rilonacept profitably.

In addition to the FDA and other regulatory agency regulations in the United States, we are subject to a variety of foreign regulatory requirements governing human clinical trials, marketing and approval for drugs, and commercial sales and distribution of drugs in foreign countries. The foreign regulatory approval process includes all of the risks associated with FDA approval as well as country-specific regulations. Whether or not we obtain FDA approval for a product in the United States, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of rilonacept in those countries.

The development of serious or life-threatening side effects with any of our product candidates would lead to delay or discontinuation of development, which could severely harm our business.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries, and discomforts, to their study doctor. Often, it is not possible to determine whether or not the drug candidate being studied caused these conditions. Various illnesses, injuries, and discomforts have been reported from time-to-time during clinical trials of our product candidates. Although our current drug candidates appeared to be generally well tolerated in clinical trials conducted to date, it is possible as we test any of them in larger, longer, and more extensive clinical programs, illnesses, injuries, and discomforts that were observed in earlier trials, as well as conditions that did not occur or went undetected in smaller previous trials, will be reported by patients. Many times, side effects are only detectable after investigational drugs are tested in large scale, Phase 3 clinical trials or, in some cases, after they are made available to patients after approval. If additional clinical experience indicates that any of our product candidates has many side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, which would severely harm our business.

Our aflibercept (VEGF Trap) is being studied for the potential treatment of certain types of cancer and our VEGF Trap-Eye candidate is being studied in diseases of the eye. There are many

potential safety concerns associated with significant blockade of vascular endothelial growth factor, or VEGF. These serious and potentially life-threatening risks, based on the clinical and preclinical experience of systemically delivered VEGF inhibitors, including the systemic delivery of the VEGF Trap, include bleeding, hypertension, and proteinuria. These serious side effects and other serious side effects have been reported in our systemic VEGF Trap studies in cancer and diseases of the eye. In addition, patients given infusions of any protein, including the VEGF Trap delivered through intravenous administration, may develop severe hypersensitivity reactions or infusion reactions. Other VEGF blockers have reported side effects that became evident only after large scale trials or after marketing approval and large number of patients were treated. These include side effects that we have not yet seen in our trials such as heart attack and stroke. These and other complications or side effects could harm the development of aflibercept for the treatment of cancer or the VEGF Trap-Eye for the treatment of diseases of the eye.

It is possible that safety or tolerability concerns may arise as we continue to test rilonacept in patients with inflammatory diseases and disorders. Like cytokine antagonists such as Kineret ® (Amgen Inc.), Enbrel ® (Immunex Corporation), and Remicade ® (Centocor, Inc.), rilonacept affects the immune defense system of the body by blocking some of its functions. Therefore, rilonacept may interfere with the body's ability to fight infections. Treatment with Kineret ® (Amgen), a medication that works through the inhibition of IL-1, has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking rilonacept. One subject with adult Still's diseases in a study of rilonacept developed an infection in his elbow with mycobacterium intracellulare. The patient was on chronic glucocorticoid treatment for Still's disease. The infection occurred after an intraarticular glucocorticoid injection into the elbow and subsequent local exposure to a suspected source of mycobacteria. One patient with polymayalgia rheumatica in another study developed bronchitis/sinusitis, which resulted in hospitalization. One patient in an open-label study of rilonacept in CAPS developed sinusitis and streptococcus pneumoniae meningitis and subsequently died. In addition, patients given infusions of rilonacept have developed hypersensitivity reactions or infusion reactions. These or other complications or side effects could impede or result in us abandoning the development of rilonacept.

Our product candidates in development are recombinant proteins that could cause an immune response, resulting in the creation of harmful or neutralizing antibodies against the therapeutic protein.

In addition to the safety, efficacy, manufacturing, and regulatory hurdles faced by our product candidates, the administration of recombinant proteins frequently causes an immune response, resulting in the creation of antibodies against the therapeutic protein. The antibodies can have no effect or can totally neutralize the effectiveness of the protein, or require that higher doses be used to obtain a therapeutic effect. In some cases, the antibody can cross react with the patient's own proteins, resulting in an "auto-immune" type disease. Whether antibodies will be created can often not be predicted from preclinical or clinical experiments, and their detection or appearance is often delayed, so that there can be no assurance that neutralizing antibodies will not be detected at a later date — in some cases even after pivotal clinical trials have been completed. Of the clinical study subjects who received rilonacept for rheumatoid arthritis and other indications, fewer than 5% of patients developed antibodies and no side effects related to antibodies were observed. Using a very sensitive test, approximately 40% of the patients in the CAPS pivotal study tested positive at least once for low levels of antibodies to rilonacept.

Again, no side effects related to antibodies were observed and there were no observed effects on drug efficacy or drug levels. However, it is possible that as we continue to test aflibercept and VEGF Trap-Eye with more sensitive assays in different patient populations and larger clinical trials, we will find that subjects given aflibercept and VEGF Trap-Eye develop antibodies to these product candidates, and may also experience side effects related to the antibodies, which could adversely impact the development of such candidates.

We may be unable to formulate or manufacture our product candidates in a way that is suitable for clinical or commercial use.

Changes in product formulations and manufacturing processes may be required as product candidates progress in clinical development and are ultimately commercialized. For example, we are currently testing a new formulation of the VEGF Trap-Eye. If we are unable to develop suitable product formulations or manufacturing processes to support large scale clinical testing of our product candidates, including aflibercept, VEGF Trap-Eye, and rilonacept, we may be unable to supply necessary materials for our clinical trials, which would delay the development of our product candidates. Similarly, if we are unable to supply sufficient quantities of our product or develop product formulations suitable for commercial use, we will not be able to successfully commercialize our product candidates.

Risks Related to Intellectual Property

If we cannot protect the confidentiality of our trade secrets or our patents are insufficient to protect our proprietary rights, our business and competitive position will be harmed.

Our business requires using sensitive and proprietary technology and other information that we protect as trade secrets. We seek to prevent improper disclosure of these trade secrets through confidentiality agreements. If our trade secrets are improperly exposed, either by our own employees or our collaborators, it would help our competitors and adversely affect our business. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our rights are covered by valid and enforceable patents or are effectively maintained as trade secrets. The patent position of biotechnology companies involves complex legal and factual questions and, therefore, enforceability cannot be predicted with certainty. Our patents may be challenged, invalidated, or circumvented. Patent applications filed outside the United States may be challenged by third parties who file an opposition. Such opposition proceedings are increasingly common in the European Union and are costly to defend. We have patent applications that are being opposed and it is likely that we will need to defend additional patent applications in the future. Our patent rights may not provide us with a proprietary position or competitive advantages against competitors. Furthermore, even if the outcome is favorable to us, the enforcement of our intellectual property rights can be extremely expensive and time consuming.

We may be restricted in our development and/or commercialization activities by, and could be subject to damage awards if we are found to have infringed, third party patents or other proprietary rights.

Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties. Other parties may allege that they have

blocking patents to our products in clinical development, either because they claim to hold proprietary rights to the composition of a product or the way it is manufactured or used. Moreover, other parties may allege that they have blocking patents to antibody products made using our *VelocImmune* technology, either because of the way the antibodies are discovered or produced or because of a proprietary position covering an antibody or the antibody's target.

We are aware of patents and pending applications owned by Genentech that claim certain chimeric VEGF receptor compositions. Although we do not believe that aflibercept or the VEGF Trap-Eye infringes any valid claim in these patents or patent applications, Genentech could initiate a lawsuit for patent infringement and assert its patents are valid and cover aflibercept or the VEGF Trap-Eye. Genentech may be motivated to initiate such a lawsuit at some point in an effort to impair our ability to develop and sell aflibercept or the VEGF Trap-Eye, which represents a potential competitive threat to Genentech's VEGF-binding products and product candidates. An adverse determination by a court in any such potential patent litigation would likely materially harm our business by requiring us to seek a license, which may not be available, or resulting in our inability to manufacture, develop and sell aflibercept or the VEGF Trap-Eye or in a damage award.

Any patent holders could sue us for damages and seek to prevent us from manufacturing, selling, or developing our drug candidates, and a court may find that we are infringing validly issued patents of third parties. In the event that the manufacture, use, or sale of any of our clinical candidates infringes on the patents or violates other proprietary rights of third parties, we may be prevented from pursuing product development, manufacturing, and commercialization of our drugs and may be required to pay costly damages. Such a result may materially harm our business, financial condition, and results of operations. Legal disputes are likely to be costly and time consuming to defend.

We seek to obtain licenses to patents when, in our judgment, such licenses are needed. If any licenses are required, we may not be able to obtain such licenses on commercially reasonable terms, if at all. The failure to obtain any such license could prevent us from developing or commercializing any one or more of our product candidates, which could severely harm our business.

Regulatory and Litigation Risks

If we do not obtain regulatory approval for our product candidates, we will not be able to market or sell them.

We cannot sell or market products without regulatory approval. If we do not obtain and maintain regulatory approval for our product candidates, the value of our company and our results of operations will be harmed. In the United States, we must obtain and maintain approval from the United States Food and Drug Administration (FDA) for each drug we intend to sell. Obtaining FDA approval is typically a lengthy and expensive process, and approval is highly uncertain. Foreign governments also regulate drugs distributed in their country and approval in any country is likely to be a lengthy and expensive process, and approval is highly uncertain. None of our product candidates has ever received regulatory approval to be marketed and sold in the United States or any other country. We may never receive regulatory approval for any of our product candidates.

Before approving a new drug or biologic product, the FDA requires that the facilities at which the product will be manufactured be in compliance with current good manufacturing practices, or cGMP requirements. Manufacturing product candidates in compliance with these regulatory requirements is complex, time-consuming, and expensive. To be successful, our products must be manufactured for development, following approval, in commercial quantities, in compliance with regulatory requirements, and at competitive costs. If we or any of our product collaborators or third-party manufacturers, product packagers, or labelers are unable to maintain regulatory compliance, the FDA can impose regulatory sanctions, including, among other things, refusal to approve a pending application for a new drug or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition, and results of operations may be materially harmed.

If the testing or use of our products harms people, we could be subject to costly and damaging product liability claims.

The testing, manufacturing, marketing, and sale of drugs for use in people expose us to product liability risk. Any informed consent or waivers obtained from people who sign up for our clinical trials may not protect us from liability or the cost of litigation. Our product liability insurance may not cover all potential liabilities or may not completely cover any liability arising from any such litigation. Moreover, we may not have access to liability insurance or be able to maintain our insurance on acceptable terms.

Our operations may involve hazardous materials and are subject to environmental, health, and safety laws and regulations. We may incur substantial liability arising from our activities involving the use of hazardous materials.

As a biopharmaceutical company with significant manufacturing operations, we are subject to extensive environmental, health, and safety laws and regulations, including those governing the use of hazardous materials. Our research and development and manufacturing activities involve the controlled use of chemicals, viruses, radioactive compounds, and other hazardous materials. The cost of compliance with environmental, health, and safety regulations is substantial. If an accident involving these materials or an environmental discharge were to occur, we could be held liable for any resulting damages, or face regulatory actions, which could exceed our resources or insurance coverage.

Changes in the securities laws and regulations have increased, and are likely to continue to increase, our costs.

The Sarbanes-Oxley Act of 2002, which became law in July 2002, has required changes in some of our corporate governance, securities disclosure and compliance practices. In response to the requirements of that Act, the SEC and the NASDAQ Stock Market have promulgated new rules and listing standards covering a variety of subjects. Compliance with these new rules and listing standards has increased our legal costs, and significantly increased our accounting and auditing costs, and we expect these costs to continue. These developments may make it more difficult and more expensive for us to obtain directors' and officers' liability insurance. Likewise, these developments may make it more difficult for us to attract and retain qualified

members of our board of directors, particularly independent directors, or qualified executive officers.

In future years, if we or our independent registered public accounting firm are unable to conclude that our internal control over financial reporting is effective, the market value of our common stock could be adversely affected.

As directed by Section 404 of the Sarbanes-Oxley Act of 2002, the SEC adopted rules requiring public companies to include a report of management on the Company's internal control over financial reporting in their annual reports on Form 10-K that contains an assessment by management of the effectiveness of our internal control over financial reporting. In addition, the independent registered public accounting firm auditing our financial statements must attest to and report on management's assessment and on the effectiveness of our internal control over financial reporting. Our independent registered public accounting firm provided us with an unqualified report as to our assessment and the effectiveness of our internal control over financial reporting as of December 31, 2006, which report was included in our Annual Report on Form 10-K. However, we cannot assure you that management or our independent registered public accounting firm will be able to provide such an assessment or unqualified report as of future year-ends. In this event, investors could lose confidence in the reliability of our financial statements, which could result in a decrease in the market value of our common stock. In addition, if it is determined that deficiencies in the design or operation of internal controls exist and that they are reasonably likely to adversely affect our ability to record, process, summarize, and report financial information, we would likely incur additional costs to remediate these deficiencies and the costs of such remediation could be material.

Risks Related to Our Dependence on Third Parties

If our collaboration with sanofi-aventis for aflibercept (VEGF Trap) is terminated, our business operations and our ability to develop, manufacture, and commercialize aflibercept in the time expected, or at all, would be harmed.

We rely heavily on sanofi-aventis to assist with the development of the aflibercept program. Sanofi-aventis funds all of the development expenses incurred by both companies in connection with the aflibercept program. If the aflibercept program continues, we will rely on sanofi-aventis to assist with funding the aflibercept program, provide commercial manufacturing capacity, enroll and monitor clinical trials, obtain regulatory approval, particularly outside the United States, and provide sales and marketing support. While we cannot assure you that aflibercept will ever be successfully developed and commercialized, if sanofi-aventis does not perform its obligations in a timely manner, or at all, our ability to develop, manufacture, and commercialize aflibercept in cancer indications will be significantly adversely affected. Sanofi-aventis has the right to terminate its collaboration agreement with us at any time upon twelve months advance notice. If sanofi-aventis were to terminate its collaboration agreement with us, we would not have the resources or skills to replace those of our partner, which could cause significant delays in the development and/or manufacture of aflibercept and result in substantial additional costs to us. We have no sales, marketing, or distribution capabilities and would have to develop or outsource these capabilities. Termination of the sanofi-aventis collaboration agreement would create substantial new and additional risks to the successful development of the aflibercept program.

If our collaboration with Bayer HealthCare for the VEGF Trap-Eye is terminated, our business operations and our ability to develop, manufacture, and commercialize the VEGF Trap-Eye in the time expected, or at all, would be harmed.

We rely heavily on Bayer HealthCare to assist with the development of the VEGF Trap-Eye. Under our agreement with them, Bayer HealthCare is required to fund approximately half of the development expenses incurred by both companies in connection with the global VEGF Trap-Eye development program. If the VEGF Trap-Eye program continues, we will rely on Bayer HealthCare to assist with funding the VEGF Trap-Eye development program, provide assistance with the enrollment and monitoring of clinical trials conducted outside the United States, obtaining regulatory approval outside the United States, and provide sales, marketing and commercial support for the product outside the United States. In particular, Bayer HealthCare has responsibility for selling VEGF Trap-Eye outside the United States using its sales force. While we cannot assure you that the VEGF Trap-Eye will ever be successfully developed and commercialized, if Bayer HealthCare does not perform its obligations in a timely manner, or at all, our ability to develop, manufacture, and commercialize the VEGF Trap-Eye outside the United States will be significantly adversely affected. Bayer HealthCare has the right to terminate its collaboration agreement with us at any time upon six or twelve months advance notice, depending on the circumstances giving rise to termination. If Bayer HealthCare were to terminate its collaboration agreement with us, we would not have the resources or skills to replace those of our partner, which could cause significant delays in the development and/or commercialization of the VEGF Trap-Eye outside the United States and result in substantial additional costs to us. We have no sales, marketing, or distribution capabilities and would have to develop or outsource these capabilities outside the United States. Termination of the Bayer HealthCare collaboration agreement would create substantial new and additional risks to the successful development of the VEGF Trap-Eye development program.

Our collaborators and service providers may fail to perform adequately in their efforts to support the development, manufacture, and commercialization of our drug candidates.

We depend upon third-party collaborators, including sanofi-aventis, Bayer HealthCare, and service providers such as clinical research organizations, outside testing laboratories, clinical investigator sites, and third-party manufacturers and product packagers and labelers, to assist us in the development of our product candidates. If any of our existing collaborators or service providers breaches or terminates its agreement with us or does not perform its development or manufacturing services under an agreement in a timely manner or at all, we could experience additional costs, delays, and difficulties in the development or ultimate commercialization of our product candidates.

Risks Related to the Manufacture of Our Product Candidates

We have limited manufacturing capacity, which could inhibit our ability to successfully develop or commercialize our drugs.

Our manufacturing facility is likely to be inadequate to produce sufficient quantities of product for commercial sale. We intend to rely on our corporate collaborators, as well as contract manufacturers, to produce the large quantities of drug material needed for commercialization of

our products. We rely entirely on third-party manufacturers for filling and finishing services. We will have to depend on these manufacturers to deliver material on a timely basis and to comply with regulatory requirements. If we are unable to supply sufficient material on acceptable terms, or if we should encounter delays or difficulties in our relationships with our corporate collaborators or contract manufacturers, our business, financial condition, and results of operations may be materially harmed.

We may expand our own manufacturing capacity to support commercial production of active pharmaceutical ingredients, or API, for our product candidates. This will require substantial additional funds, and we will need to hire and train significant numbers of employees and managerial personnel to staff our facility. Start-up costs can be large and scale-up entails significant risks related to process development and manufacturing yields. We may be unable to develop manufacturing facilities that are sufficient to produce drug material for clinical trials or commercial use. In addition, we may be unable to secure adequate filling and finishing services to support our products. As a result, our business, financial condition, and results of operations may be materially harmed.

We may be unable to obtain key raw materials and supplies for the manufacture of our product candidates. In addition, we may face difficulties in developing or acquiring production technology and managerial personnel to manufacture sufficient quantities of our product candidates at reasonable costs and in compliance with applicable quality assurance and environmental regulations and governmental permitting requirements.

If any of our clinical programs are discontinued, we may face costs related to the unused capacity at our manufacturing facilities.

We have large-scale manufacturing operations in Rensselaer, New York. We use our facilities to produce bulk product for clinical and preclinical candidates for ourselves and our collaborations. If our clinical candidates are discontinued, we will have to absorb one hundred percent of related overhead costs and inefficiencies.

Certain of our raw materials are single-sourced from third parties; third-party supply failures could adversely affect our ability to supply our products.

Certain raw materials necessary for manufacturing and formulation of our product candidates are provided by single-source unaffiliated third-party suppliers. We would be unable to obtain these raw materials for an indeterminate period of time if these third-party single-source suppliers were to cease or interrupt production or otherwise fail to supply these materials or products to us for any reason, including due to regulatory requirements or action, due to adverse financial developments at or affecting the supplier, or due to labor shortages or disputes. This, in turn, could materially and adversely affect our ability to manufacture our product candidates for use in clinical trials, which could materially and adversely affect our business and future prospects.

Also, certain of the raw materials required in the manufacturing and the formulation of our clinical candidates may be derived from biological sources, including mammalian tissues, bovine serum, and human serum albumin. There are certain European regulatory restrictions on using these biological source materials. If we are required to substitute for these sources to comply

with European regulatory requirements, our clinical development activities may be delayed or interrupted.

Risks Related to Commercialization of Products

If we are unable to establish sales, marketing, and distribution capabilities, or enter into agreements with third parties to do so, we will be unable to successfully market and sell future products.

We have no sales or distribution personnel or capabilities and have only a small staff with marketing capabilities. If we are unable to obtain those capabilities, either by developing our own organizations or entering into agreements with service providers, we will not be able to successfully sell any products that we may obtain regulatory approval for and bring to market in the future. In that event, we will not be able to generate significant revenue, even if our product candidates are approved. We cannot guarantee that we will be able to hire the qualified sales and marketing personnel we need or that we will be able to enter into marketing or distribution agreements with third-party providers on acceptable terms, if at all. Under the terms of our collaboration agreement with sanofi-aventis, we currently rely on sanofi-aventis for sales, marketing, and distribution of aflibercept in cancer indications, should it be approved in the future by regulatory authorities for marketing. We will have to rely on a third party or devote significant resources to develop our own sales, marketing, and distribution capabilities for our other product candidates, including the VEGF Trap-Eye in the United States, and we may be unsuccessful in developing our own sales, marketing, and distribution organization.

Even if our product candidates are approved for marketing, their commercial success is highly uncertain because our competitors have received approval for products with the same mechanism of action, and competitors may get to the marketplace before we do with better or lower cost drugs or the market for our product candidates may be too small to support commercialization or sufficient profitability.

There is substantial competition in the biotechnology and pharmaceutical industries from pharmaceutical, biotechnology, and chemical companies. Many of our competitors have substantially greater research, preclinical and clinical product development and manufacturing capabilities, and financial, marketing, and human resources than we do. Our smaller competitors may also enhance their competitive position if they acquire or discover patentable inventions, form collaborative arrangements, or merge with large pharmaceutical companies. Even if we achieve product commercialization, our competitors have achieved, and may continue to achieve, product commercialization before our products are approved for marketing and sale.

Genentech has an approved VEGF antagonist, Avastin ® (Genentech), on the market for treating certain cancers and many different pharmaceutical and biotechnology companies are working to develop competing VEGF antagonists, including Novartis, OSI Pharmaceuticals, and Pfizer. Many of these molecules are farther along in development than aflibercept and may offer competitive advantages over our molecule . Novartis has an ongoing Phase 3 clinical development program evaluating an orally delivered VEGF tyrosine kinase inhibitor in different cancer settings. Each of Pfizer and Onyx Pharmaceuticals (together with its partner Bayer HealthCare) has received approval from the FDA to market and sell an oral medication that targets tumor cell growth and new vasculature formation that fuels the growth of tumors. The

marketing approvals for Genentech's VEGF antagonist, Avastin ® (Genentech), and their extensive, ongoing clinical development plan for Avastin ® (Genentech) in other cancer indications, may make it more difficult for us to enroll patients in clinical trials to support aflibercept and to obtain regulatory approval of aflibercept in these cancer settings. This may delay or impair our ability to successfully develop and commercialize aflibercept. In addition, even if aflibercept is ever approved for sale for the treatment of certain cancers, it will be difficult for our drug to compete against Avastin ® (Genentech) and the FDA approved kinase inhibitors, because doctors and patients will have significant experience using these medicines. In addition, an oral medication may be considerably less expensive for patients than a biologic medication, providing a competitive advantage to companies that market such products.

The market for eye disease products is also very competitive. Novartis and Genentech are collaborating on the commercialization and further development of a VEGF antibody fragment (Lucentis ®) for the treatment of age-related macular degeneration (wet AMD) and other eye indications that was approved by the FDA in June 2006. OSI Pharmaceuticals and Pfizer are marketing an approved VEGF inhibitor for wet AMD. Many other companies are working on the development of product candidates for the potential treatment of wet AMD that act by blocking VEGF, VEGF receptors, and through the use of soluble ribonucleic acids (sRNAs) that modulate gene expression. In addition, ophthalmologists are using off-label a third-party reformatted version of Genentech's approved VEGF antagonist, Avastin ® , with success for the treatment of wet AMD. The National Eye Institute recently has received funding for a Phase 3 trial to compare Lucentis ® (Genentech) to Avastin ® (Genentech) in the treatment of wet AMD. The marketing approval of Lucentis ® (Genentech) and the potential off-label use of Avastin ® (Genentech) make it more difficult for us to enroll patients in our clinical trials and successfully develop the VEGF Trap-Eye. Even if the VEGF Trap-Eye is ever approved for sale for the treatment of eye diseases, it may be difficult for our drug to compete against Lucentis ® (Genentech), because doctors and patients will have significant experience using this medicine. Moreover, the relatively low cost of therapy with Avastin ® (Genentech) in patients with wet AMD presents a further competitive challenge in this indication.

The availability of highly effective FDA approved TNF-antagonists such as Enbrel ® (Immunex), Remicade ® (Centocor), and Humira ® (Abbott Biotechnology Ltd.), and the IL-1 receptor antagonist Kineret ® (Amgen), and other marketed therapies makes it more difficult to successfully develop and commercialize rilonacept. This is one of the reasons we discontinued the development of rilonacept in adult rheumatoid arthritis. In addition, even if rilonacept is ever approved for sale, it will be difficult for our drug to compete against these FDA approved TNF-antagonists in indications where both are useful because doctors and patients will have significant experience using these effective medicines. Moreover, in such indications these approved therapeutics may offer competitive advantages over rilonacept, such as requiring fewer injections.

There are both small molecules and antibodies in development by third parties that are designed to block the synthesis of interleukin-1 or inhibit the signaling of interleukin-1. For example, Eli Lilly and Company and Novartis are each developing antibodies to interleukin-1 and Amgen is developing an antibody to the interleukin-1 receptor. It has been reported that Novartis has commenced advanced clinical testing of its IL-1 antibody in Muckle-Wells Syndrome, which is part of the group of rare genetic diseases called CAPS. Novartis' IL-1 antibody and these other drug candidates could offer competitive advantages over rilonacept.

The successful development of these competing molecules could delay or impair our ability to successfully develop and commercialize rilonacept. For example, we may find it difficult to enroll patients in clinical trials for rilonacept if the companies developing these competing interleukin-1 inhibitors commence clinical trials in the same indications.

We are developing rilonacept for the treatment of a group of rare diseases associated with mutations in the *CIAS* 1 gene. These rare genetic disorders affect a small group of people, estimated to be between several hundred and a few thousand. There may be too few patients with these genetic disorders to profitably commercialize rilonacept in this indication.

The successful commercialization of our product candidates will depend on obtaining coverage and reimbursement for use of these products from third-party payers and these payers may not agree to cover or reimburse for use of our products.

Our products, if commercialized, may be significantly more expensive than traditional drug treatments. Our future revenues and profitability will be adversely affected if United States and foreign governmental, private third-party insurers and payers, and other third-party payers, including Medicare and Medicaid, do not agree to defray or reimburse the cost of our products to the patients. If these entities refuse to provide coverage and reimbursement with respect to our products or provide an insufficient level of coverage and reimbursement, our products may be too costly for many patients to afford them, and physicians may not prescribe them. Many third-party payers cover only selected drugs, making drugs that are not preferred by such payer more expensive for patients, and require prior authorization or failure on another type of treatment before covering a particular drug. Payers may especially impose these obstacles to coverage on higher-priced drugs, as our product candidates are likely to be.

We are seeking approval to market rilonacept for the treatment of a group of rare genetic disorders called CAPS. There may be too few patients with CAPS to profitably commercialize rilonacept. Physicians may not prescribe rilonacept and CAPS patients may not be able to afford rilonacept if third party payers do not agree to reimburse the cost of rilonacept therapy and this would adversely affect our ability to commercialize rilonacept profitably.

In addition to potential restrictions on coverage, the amount of reimbursement for our products may also reduce our profitability. In the United States, there have been, and we expect will continue to be, actions and proposals to control and reduce healthcare costs. Government and other third-party payers are challenging the prices charged for healthcare products and increasingly limiting, and attempting to limit, both coverage and level of reimbursement for prescription drugs.

Since our products, including rilonacept, will likely be too expensive for most patients to afford without health insurance coverage, if our products are unable to obtain adequate coverage and reimbursement by third-party payers our ability to successfully commercialize our product candidates may be adversely impacted. Any limitation on the use of our products or any decrease in the price of our products will have a material adverse effect on our ability to achieve profitability.

In certain foreign countries, pricing, coverage and level of reimbursement of prescription drugs are subject to governmental control, and we may be unable to negotiate coverage, pricing,

and reimbursement on terms that are favorable to us. In some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Our results of operations may suffer if we are unable to market our products in foreign countries or if coverage and reimbursement for our products in foreign countries is limited.

Risk Related to Employees

We are dependent on our key personnel and if we cannot recruit and retain leaders in our research, development, manufacturing, and commercial organizations, our business will be harmed.

We are highly dependent on certain of our executive officers. If we are not able to retain any of these persons or our Chairman, our business may suffer. In particular, we depend on the services of P. Roy Vagelos, M.D., the Chairman of our board of directors, Leonard Schleifer, M.D., Ph.D., our President and Chief Executive Officer, George D. Yancopoulos, M.D., Ph.D., our Executive Vice President, Chief Scientific Officer and President, Regeneron Research Laboratories, and Neil Stahl, Ph.D., our Senior Vice President, Research and Development Sciences. There is intense competition in the biotechnology industry for qualified scientists and managerial personnel in the development, manufacture, and commercialization of drugs. We may not be able to continue to attract and retain the qualified personnel necessary for developing our business.

Risks Related to Our Common Stock

Our stock price is extremely volatile.

There has been significant volatility in our stock price and generally in the market prices of biotechnology companies' securities. Various factors and events may have a significant impact on the market price of our common stock. These factors include, by way of example:

- progress, delays, or adverse results in clinical trials;
- announcement of technological innovations or product candidates by us or competitors;
- fluctuations in our operating results;
- public concern as to the safety or effectiveness of our product candidates;
- developments in our relationship with collaborative partners;
- developments in the biotechnology industry or in government regulation of healthcare;
- large sales of our common stock by our executive officers, directors, or significant shareholders;
- arrivals and departures of key personnel; and
- general market conditions.

The trading price of our common stock has been, and could continue to be, subject to wide fluctuations in response to these and other factors, including the sale or attempted sale of a large amount of our common stock in the market. Broad market fluctuations may also adversely affect the market price of our common stock.

Future sales of our common stock by our significant shareholders or us may depress our stock price and impair our ability to raise funds in new share offerings.

A small number of our shareholders beneficially own a substantial amount of our common stock. As of September 30, 2007, our seven largest shareholders beneficially owned 42.3% of our outstanding shares of Common Stock, assuming, in the case of Leonard S. Schleifer, M.D. Ph.D., our Chief Executive Officer, and P. Roy Vagelos, M.D., our Chairman, the conversion of their Class A Stock into Common Stock and the exercise of all options held by them which are exercisable within 60 days of September 30, 2007. As of September 30, 2007, sanofi-aventis owned 2,799,552 shares of Common Stock, representing approximately 4.4% of the shares of Common Stock then outstanding. Under our stock purchase agreement with sanofi-aventis, sanofi-aventis may sell no more than 500,000 of these shares in any calendar quarter. If sanofi-aventis, or our other significant shareholders or we, sell substantial amounts of our Common Stock in the public market, or the perception that such sales may occur exists, the market price of our Common Stock could fall. Sales of Common Stock by our significant shareholders, including sanofi-aventis, also might make it more difficult for us to raise funds by selling equity or equity-related securities in the future at a time and price that we deem appropriate.

Our existing shareholders may be able to exert significant influence over matters requiring shareholder approval.

Holders of Class A Stock, who are generally the shareholders who purchased their stock from us before our initial public offering, are entitled to ten votes per share, while holders of Common Stock are entitled to one vote per share. As of September 30, 2007, holders of Class A Stock held 26.2% of the combined voting power of all of Common Stock and Class A Stock then outstanding. These shareholders, if acting together, would be in a position to significantly influence the election of our directors and to effect or prevent certain corporate transactions that require majority or supermajority approval of the combined classes, including mergers and other business combinations. This may result in our company taking corporate actions that you may not consider to be in your best interest and may affect the price of our Common Stock. As of September 30, 2007:

- our current executive officers and directors beneficially owned 12.9% of our outstanding shares of Common Stock, assuming conversion of their Class A Stock into Common Stock and the exercise of all options held by such persons which are exercisable within 60 days of September 30, 2007, and 30.2% of the combined voting power of our outstanding shares of Common Stock and Class A Stock, assuming the exercise of all options held by such persons which are exercisable within 60 days of September 30, 2007; and
- our seven largest shareholders beneficially owned 42.3% of our outstanding shares of Common Stock, assuming, in the case of Leonard S. Schleifer, M.D., Ph.D., our Chief Executive Officer, and P. Roy Vagelos, M.D., our Chairman, the conversion of their

Class A Stock into Common Stock and the exercise of all options held by them which are exercisable within 60 days of September 30, 2007. In addition, these seven shareholders held 49.6% of the combined voting power of our outstanding shares of Common Stock and Class A Stock, assuming the exercise of all options held by our Chief Executive Officer and our Chairman which are exercisable within 60 days of September 30, 2007.

The anti-takeover effects of provisions of our charter, by-laws, and of New York corporate law, could deter, delay, or prevent an acquisition or other "change in control" of us and could adversely affect the price of our common stock.

Our amended and restated certificate of incorporation, our by-laws and the New York Business Corporation Law contain various provisions that could have the effect of delaying or preventing a change in control of our company or our management that shareholders may consider favorable or beneficial. Some of these provisions could discourage proxy contests and make it more difficult for you and other shareholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions include:

- authorization to issue "blank check" preferred stock, which is preferred stock that can be created and issued by the board of directors without prior shareholder approval, with rights senior to those of our common shareholders;
- a staggered board of directors, so that it would take three successive annual meetings to replace all of our directors;
- a requirement that removal of directors may only be effected for cause and only upon the affirmative vote of at least eighty percent (80%) of the outstanding shares entitled to vote for directors, as well as a requirement that any vacancy on the board of directors may be filled only by the remaining directors;
- any action required or permitted to be taken at any meeting of shareholders may be taken without a meeting, only if, prior to such action, all of our shareholders consent, the effect of which is to require that shareholder action may only be taken at a duly convened meeting;
- any shareholder seeking to bring business before an annual meeting of shareholders must provide timely notice of this intention in writing and meet various other requirements; and
- under the New York Business Corporation Law, a plan of merger or consolidation of the Company must be approved by two-thirds of the votes of all outstanding shares entitled to vote thereon. See the risk factor immediately above captioned *"Our existing shareholders may be able to exert significant influence over matters requiring shareholder approval."*

In addition, we have a Change in Control Severance Plan and our chief executive officer has an employment agreement that provides severance benefits in the event our officers are terminated as a result of a change in control of the Company. Many of our stock options issued under our 2000 Long-Term Incentive Plan may become fully vested in connection with a "change in control" of our company, as defined in the plan.

Item 6. Exhibits

(a) Exhibits

Exhibit Number	Description
10.1*	- First Amendment to Lease, by and between BMR-Landmark at Eastview LLC and Regeneron Pharmaceuticals, Inc., effective as of October 24, 2007.
12.1	- Statement re: computation of ratio of earnings to combined fixed charges.
31.1	- Certification of CEO pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934.
31.2	- Certification of CFO pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934.
32	- Certification of CEO and CFO pursuant to 18 U.S.C. Section 1350.

* Portions of this document have been omitted and filed separately with the Commission pursuant to requests for confidential treatment pursuant to Rule 24b-2.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Regeneron Pharmaceuticals, Inc.

Date: November 7, 2007

By: /s/ Murray A. Goldberg
Murray A. Goldberg
Senior Vice President, Finance & Administration,
Chief Financial Officer, Treasurer, and
Assistant Secretary
(Principal Financial Officer and
Duly Authorized Officer)

Exhibit 10.1

* Confidential Materials Omitted And Filed Separately With The Securities And Exchange Commission. Asterisks Denote Omissions.

FIRST AMENDMENT TO LEASE

This **First Amendment to Lease** (this " **Amendment** ") is entered into as of September 14, 2007 (the " **First Amendment Date** ") by and between BMR-Landmark at Eastview LLC, a Delaware limited liability company (" **Landlord** "), and Regeneron Pharmaceuticals, Inc., a New York corporation (" **Tenant** ").

RECITALS

(A) Landlord and Tenant are parties to that certain Lease (the " **Lease** ") dated as of December 21, 2006, pursuant to which Landlord (a) leases the Premises (as defined in the Lease) to Tenant and (b) has provided Tenant an option (the " **Expansion Option** ") to expand the Premises and take occupancy of the entire New Multiple Tenant Building. All capitalized terms used but not otherwise defined herein shall have the meanings given such terms in the Lease.

(B) Tenant has delivered to Landlord the Expansion Notice.

(C) Landlord and Tenant desire to amend certain terms of the Lease, as set forth below, to reflect their understanding with respect to such terms and the addition of the Expansion Space (as defined below) to the Premises.

AGREEMENT

NOW, THEREFORE, Landlord and Tenant, in consideration of the mutual promises contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, agree as follows:

A. Amendments

1. Expansion Space . The Lease is hereby amended to include the first floor of the New Multiple Tenant Building, as depicted on Exhibit A attached to the Lease (the " **Expansion Space** "), so that such space constitutes a part of, and is included within the meaning of, the "New Multiple Tenant Building Premises", the "New Premises" and the "Premises", as such terms are used in the Lease. The Expansion Space shall be delivered to Tenant together with the rest of the New Multiple Tenant Building Premises in accordance with the terms of the Lease, so that the entire New Multiple Tenant Building will be leased to Tenant. Except as specifically provided otherwise herein or in the Lease, all of the terms and conditions set forth herein and in the Lease shall apply to the Expansion Space. The description of the Expansion Space set forth on Exhibit A attached hereto is hereby added to the description of the New Multiple Tenant Building Premises on Exhibit A to the Lease. The mere exercise by Tenant of the Expansion Option and any additional Landlord Work required to be performed to deliver possession of the Expansion Premises in the condition and on the date provided in the Lease, shall not constitute a Tenant Delay under this Lease.

2. Estimated Term Commencement Date . Section 2.6 of the Lease is hereby amended by replacing the date "March 6, 2008" where such date appears therein with the date "June 20, 2008".

3. Exhibit F. Exhibit F to the Lease is hereby amended by (i) replacing the value "$68,107,092", where such value appears in the letter therein, dated December 12, 2006, from David Surette to Steve Marshall, with the value "68,159,687" and (ii) replacing the Schedule of Values therein with the Schedule of Values attached hereto as Exhibit B.

B. Miscellaneous

1. This Amendment shall be governed by, construed and enforced in accordance with the laws of the state in which the Premises are located, without regard to such state's conflict of law principles.

2. Tenant and Landlord each represents and warrants to the other that it has had no dealings with any real estate broker or agent in connection with the negotiation of this Amendment other than Studley, Inc. ("Broker"), and that it knows of no other real estate broker or agent that is or might be entitled to a commission in connection with this Amendment. Landlord shall compensate Broker in relation to this Amendment pursuant to a separate agreement between Landlord and Broker

3. Each of Landlord and Tenant represents that, except as amended hereby, the Lease has not been modified and remains in full force and effect and the individual or those individuals signing this Amendment on behalf of Landlord or Tenant (respectively) have the power, authority and legal capacity to sign this Amendment on behalf of and to bind all entities, corporations, partnerships, limited liability companies, joint venturers or other organizations and entities on whose behalf said individual or individuals have signed.

4. This Amendment may be executed in one or more counterparts, each of which, when taken together, shall constitute one and the same document.

Remainder of Page Intentionally Left Blank.
Signature Page Follows.

IN WITNESS WHEREOF, the parties hereto have executed this Amendment as of the date first above written.

LANDLORD:

BMR-Landmark at Eastview LLC,
a Delaware limited liability company

By: /s/ Matthew G. McDevitt
Name: Matthew G. McDevitt
Title: Regional Executive Vice President

TENANT:

Regeneron Pharmaceuticals, Inc.,
a New York corporation

By: /s/ Murray A. Goldberg
Name: Murray A. Goldberg
Title: Senior Vice President, Finance & Administration and Chief Financial Officer

EXHIBIT A

EXPANSION SPACE

EXHIBIT A

EXPANSION SPACE DESCRIPTION

The Expansion Space is the entire first floor of the New Multiple Tenant Building, along with the remaining portions of the basement and penthouse. The Rentable Area of the Expansion Space shall be defined as follows:

First floor= 33,169 square feet
Basement= 1,738 square feet
Penthouse= 849 square feet
Total Rentable Area of Expansion Space= 35,756 square feet*

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* The Lease incorrectly references total Rentable Area of Expansion Space as 35,755 square feet.

EXHIBIT B

SCHEDULE OF VALUES

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Exhibit 12.1

Regeneron Pharmaceuticals, Inc.
Computation of Ratio of Earnings to Combined Fixed Charges
(Dollars in thousands)

	Years ended December 31,					Nine months ended September 30,
	2002	2003	2004	2005	2006	2007
Earnings:						
Income (loss) from continuing operations before income (loss) from equity investee	$(124,350)	$(107,395)	$41,565	$(95,456)	$(103,150)	$ (92,529)
Fixed charges	13,685	14,108	14,060	13,687	13,643	10,285
Amortization of capitalized interest	—	33	78	78	73	18
Interest capitalized	(222)	(276)	—	—	—	—
Adjusted earnings	$(110,887)	$ (93,530)	$55,703	$(81,691)	$ (89,434)	$ (82,226)
Fixed charges:						
Interest expense	$ 11,859	$ 11,932	$12,175	$ 12,046	$ 12,043	$ 9,033
Interest capitalized	222	276	—	—	—	—
Assumed interest component of rental charges	1,604	1,900	1,885	1,641	1,600	1,252
Total fixed charges	$ 13,685	$ 14,108	$14,060	$ 13,687	$ 13,643	$ 10,285
Ratio of earnings to fixed charges	(A)	(A)	3.96	(A)	(A)	(A)

(A) Due to the registrant's losses for the years ended December 31, 2002, 2003, 2005, and 2006, and for the nine months ended September 30, 2007, the ratio coverage was less than 1:1. To achieve a coverage ratio of 1:1, the registrant must generate additional earnings of the amounts shown in the table below.

	Years ended December 31,				Nine months ended September 30,
	2002	2003	2005	2006	2007
Coverage deficiency	$124,572	$107,638	$95,378	$103,077	$92,511

Exhibit 31.1

Certification of CEO Pursuant to
Rule 13a-14(a) under the Securities Exchange Act
of 1934, as Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Leonard S. Schleifer, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Regeneron Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations, and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2007

/s/ Leonard S. Schleifer
Leonard S. Schleifer, M.D., Ph.D.
President and Chief Executive Officer

Exhibit 31.2

Certification of CFO Pursuant to
Rule 13a-14(a) under the Securities Exchange Act
of 1934, as Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Murray A. Goldberg, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Regeneron Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations, and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 7, 2007

/s/ Murray A. Goldberg
Murray A. Goldberg
Senior Vice President, Finance &
Administration, Chief Financial Officer,
Treasurer, and Assistant Secretary

Exhibit 32

Certification of CEO and CFO Pursuant to
18 U.S.C. Section 1350,
As Adopted Pursuant to
Section 906 of the Sarbanes-Oxley Act of 2002

In connection with the Quarterly Report of Regeneron Pharmaceuticals, Inc. (the "Company") on Form 10-Q for the quarterly period ended September 30, 2007 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Leonard S. Schleifer, M.D., Ph.D., as Chief Executive Officer of the Company, and Murray A. Goldberg, as Chief Financial Officer of the Company, each hereby certifies, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, to the best of his knowledge, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Leonard S. Schleifer
Leonard S. Schleifer, M.D., Ph.D.
Chief Executive Officer
November 7, 2007

/s/ Murray A. Goldberg
Murray A. Goldberg
Chief Financial Officer
November 7, 2007

OBS4

International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–91) and Recommended (1–52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–91) et recommandées (1–52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del "Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas", se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–91) y Recomendadas (1–52) se encuentran reunidas en *Cumulative List No. 11, 2004* (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

Proposed International Nonproprietary Names: List 95

Publication date: 21 August 2006
Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List** 95 **Proposed INN not later than** 21 December 2006.

Dénominations communes internationales proposées: Liste 95

Date de publication:21 août 2006.
Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la **Liste** 95 **de DCI Proposées le** 21 décembre 2006 **au plus tard.**

Denominaciones Comunes Internacionales Propuestas: Lista 95

Fecha de la publicación: el 21 de agosto de 2006
Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para **la Lista** 95 **de DCI Propuestas el** 21 de diciembre de 2006 **a más tardar.**

Proposed INN (Latin, English, French, Spanish)	*Chemical name or description: Action and use: Molecular formula Chemical Abstracts Service (CAS) registry number: Graphic formula*
DCI Proposée	*Nom chimique ou description: Propriétés et indications: Formule brute Numéro dans le registre du CAS: Formule développée*
DCI Propuesta	*Nombre químico o descripción: Acción y uso: Fórmula molecular Número de registro del CAS: Fórmula desarrollada*

abagovomabum*	
abagovomab	immunoglobulin G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) *Mus musculus* monoclonal antibody OC125] *Mus musculus* monoclonal antibody ACA125, clone 3D5 gamma1 heavy chain disulfide with clone 3D5 kappa light chain; (223-223":226-226":228-228") trisdisulfide dimer *immunological agent, antineoplastic*
abagovomab	immunoglobuline G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) anticorps monoclonal murin OC125] anticorps monoclonal murin ACA125, chaîne lourde gamma1 du clone 3D5 unie par un pont disulfure à la chaîne légère kappa du clone 3D5; dimère (223-223":226-226":228-228")-trisdisulfure *agent immunologique, antinéoplasique*
abagovomab	inmunoglobulina G1, anti-idiotipo anti-[anti-(*Homo sapiens* cancer antígeno 125, CA 125, MUC-16) anticuerpo monoclonal murino OC125] anticuerpo monoclonal murino ACA125, cadena pesada gamma1 del clon 3D5 unida por un puente disulfuro a la cadena ligera kappa del clon 3D5; dímero (223-223":226-226":228-228")-trisdisulfuro *agente inmunológico, antineoplásico*

792921-10-9

Heavy chain/Chaîne lourde/Cadena pesada

```
QVKLQESGAE LARPGASVKL SCKASGYTFT NYWMQWVKQR PGQGLDWIGA  50
IYPGDGNTRY THKFKGKATL TADKSSSTAY MQLSSLASED SGVYYCARGE 100
GNYAWFAYWG QGTTVTVSSA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG 150
YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT 200
CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT 250
LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS 300
ELPIMHQDWL NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP 350
KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY 400
FVYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK         443
```

Light chain/Chaîne légère/Cadena ligera

```
DIELTQSPAS LSASVGETVT ITCQASENIY SYLAWHQQKQ GKSPQLLVYN  50
AKTLAGGVSS RFSGSGSGTH FSLKIKSLQP EDFGIYYCQH HYGILPTFGG 100
GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI 150
DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT 200
STSPIVKSFN RNEC                                        214
```

acidum iodofilticum (^{123}I)
iodofiltic acid (^{123}I)

(3*RS*)-15-[4-[^{123}I]iodophenyl]3-methylpentadecanoic acid
radiopharmaceutical

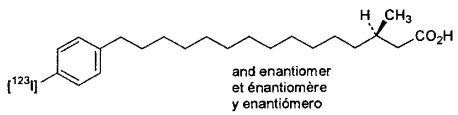
acide iodofiltique (^{123}I)

acide (3*RS*)-15-(4-[^{123}I]iodophényl)-3-méthylpentadécanoïque
radiopharmaceutique

ácido iodofiltico (^{123}I)

ácido (3*RS*)-15-(4-[^{123}I]iodofenil)-3-metilpentadecanoico
preparacion farmaceutica radiactiva

$C_{22}H_{35}{}^{123}IO_2$ 123748-56-1



and enantiomer
et énantiomère
y enantiómero

aclidinii bromidum
aclidinium bromide

(3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide
muscarinic receptor antagonist

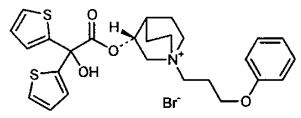
bromure d'aclidinium

bromure de (3*R*)-3-[[hydroxybis(thiophén-2-yl)acétyl]oxy]-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane
antagoniste des récepteurs muscariniques

bromuro de aclidinio

bromuro de (3R)-1-(3-fenoxipropil)-3-[(hidroxi)di(tiofen-2-il)acetiloxi]-1λ^5-azabiciclo[2.2.2]octan-1-ilio
antagonista de los receptores muscarínicos

$C_{26}H_{30}BrNO_4S_2$ 320345-99-1



afimoxifenum
afimoxifene

4-(1-{4-[2-(dimethylamino)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol
antiestrogen

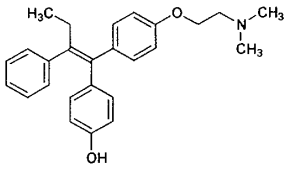
afimoxifène

4-[1-[4-[2-(diméthylamino)éthoxy]phényl]-2-phénylbut-1-ényl]phénol
antioestrogène

afimoxifeno

4-[1-[4-[2-(dimetilamino)etoxi]fenil]-2-fenilbut-1-enil]fenol
antiestrógeno

$C_{26}H_{29}NO_2$ 68392-35-8



and *Z* isomer
et l'isomère *Z*
y el isómero *Z*

afliberceptum*
aflibercept

des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 *C*-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
angiogenesis inhibitor

aflibercept

(211-211':214-214')-bisdisulfure du dimère de la dès-432-lysine-[récepteur 1 humain du facteur de croissance endothélial vasculaire-(103-204)-peptide (contenant le domaine Ig-like C2-type 2) protéine de fusion avec le récepteur 2 humain du facteur de croissance endothélial vasculaire-(206-308)-peptide (contenant un fragment du domaine Ig-like C2-type 3) protéine de fusion avec l'immunoglobuline G1 humaine-(227 résidus *C*-terminaux)-peptide (fragment Fc)]
inhibiteur de l'angiogénèse

aflibercept

(211-211':214-214')-bisdisulfuro del dímero de la des-432-lisina-[receptor 1 humano del factor de crecimiento endotelial vascular-(103-204)-péptido (que contiene el dominio Ig-like C2-tipo 2) proteína de fusión con el receptor 2 humano del factor de crecimiento endotelial vascular-(206-308)-péptido (que contiene un fragmento del dominio Ig-like C2-tipo 3) proteína de fusión con la inmunoglobulina G1 humana-(227 restos *C*-terminales)-péptido (fragmento Fc)]
inhibidor de la angiogenesis

$C_{4316}H_{6788}N_{1164}O_{1304}S_{32}$ 845771-78-0

Monomer / Monomère / Monómero

```
(SDTGRPFVEM YSEIPEIIHM TEGRELVIPC RVTSPNITVT LKKFPLDTLI) (50)
(PDGKRIIWDS RKGFIISNAT YKEIGLLTCE ATVNGHLYKT NYLTHRQTNT) (100)
(IIDVVLSPSH GIELSVGEKL VLNCTARTEL NVGIDFNWEY PSSKHQHKKL) (150)
(VNRDLKTQSG SEMKKFLSTL TIDGVTRSDQ GLYTCAASSG LMTKKNSTFV) (200)
(RVHEKDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD) (250)
(VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN) (300)
(GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL) (350)
(TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS) (400)
(RWQQGNVFSC SVMHEALHNH YTQKSLSLSP G) (431)
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
(30-79) (30'-79') (124-185) (124'-185' 211-211')
(214-214' 246-306 246'-306' 352-410 352'-410')
```

aleglitazarum
aleglitazar

(2*S*)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-benzothiophen-7-yl}propanoic acid
antidiabetic

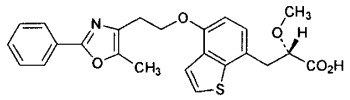
aléglitazar

acide (2*S*)-2-méthoxy-3-[4-[2-(5-méthyl-2-phényl-1,3-oxazol-4-yl)=éthoxy]-1-benzothiophén-7-yl]propanoïque
antidiabétique

aleglitazar

ácido (2*S*)-3-{4-[2-(2-fenil-1,3-oxazol-5-metil-4-il)etoxi]-1-benzotiofen-7-il}-2-metoxipropanoico
hipoglucemiante

$C_{24}H_{23}NO_5S$ 475479-34-6



alferminogenum tadenovecum*
alferminogene tadenovec

Recombinant human adenovirus 5 (replication-deficient, E1-deleted) containing a human fibroblast growth factor-4 cDNA sequence driven by a cytomegalovirus promoter
gene therapy product - stimulates angiogenesis

alferminogène tadénovec

adénovirus 5 humain recombinant (réplication-déficient, région E1-supprimée) contenant la séquence ADN-copie du facteur 4 de croissance du fibroblaste humain sous contrôle d'un promoteur de cytomégalovirus
produit de thérapie génique stimulateur de l'angiogénèse

alferminogén tadenovec

adenovirus 5 humano recombinante (replicación-deficiente, con delección E1) que contiene la secuencia DNA-copia del factor-4 de crecimiento de fibroblastos humanos controlado por un promotor de citomegalovirus
producto para genoterapia,estimulante de la angiogénesis

473553-86-5

OBSS

Expert Opinion

VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

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Background: Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD. In addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2. *Objective*: To review the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD. *Methods*: Literature review. *Results/conclusion*: VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. Two Phase III clinical trials (VIEW-1 and VIEW-2) comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide vital insight into the clinical applicability of this drug.

Keywords: aflibercept, AMD, angiogenesis, neovascularization, VEGF, VEGF inhibition, VEGF Trap

Expert Opin. Investig. Drugs (2009) 18(10):1-8

1. Introduction

Age-related macular degeneration (AMD) affects > 1.75 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million [1]. Worldwide, AMD is estimated to affect 14 million people [2]. While the vast majority of patients suffering from AMD have the dry form, ~ 80 – 90% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease [3]. Until recently, healthcare professionals had few options when it came to treating neovascular AMD. For many years, subfoveal choroidal neovascularization (CNV) was treated with argon laser therapy according to guidelines from the Macular Photocoagulation Study [4-12]. This treatment, in the setting of subfoveal disease, was unsatisfactory for a number of reasons, including the limited benefits in visual stabilization and the high risk of inducing central vision deficits [13]. Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photosensitizing dye (verteporfin) to selectively target CNV. While more efficacious than previous treatments, patients receiving PDT failed to recover vision and continued to experience a decline in visual acuity [14] and the treatment was of questionable cost effectiveness [15].

The more recent development of agents that inhibit VEGF has largely supplanted these previous treatments. The pathogenesis of CNV in the setting of

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AMD is complex; however, there is overwhelming evidence that VEGF is a predominant mediator in its genesis. VEGF receptors are expressed by a number of important cell types in the eye, including vascular endothelial cells, choroidal fibroblasts, retinal pigment epithelial cells and inflammatory cells attracted by hypoxia [16-19]. Higher levels of VEGF expression have been demonstrated in animal models [20,21] and human studies of eyes with AMD [17,22-24] and antagonism of VEGF in both settings have definitively demonstrated inhibition of neovascularization and vascular permeability. VEGF-A is the predominant member of the VEGF family targeted by drugs currently in widespread use; however, the group is also comprised of VEGF-B, VEGF-C, VEFG-D and placental growth factors-1 and -2.

Systemic administration of bevacizumab is effective against neovascular AMD; however, systemic complications limit its use [25]. Accordingly, all anti-VEGF agents for neovascular AMD are administered only by intravitreal injection. The two largest studies examining anti-VEGF therapy, the MARINA [26] and the ANCHOR [27,28] trials, were randomized, controlled, double-masked Phase III clinical trials that together evaluated monthly ranibizumab for the treatment of all types of neovascular AMD. In both trials, 94% of patients with neovascular AMD lost fewer than 15 letters of visual acuity at 12 and 24 months when treated with ranibizumab. Surprisingly, as many as 40% of patients in the two trials improved by > 15 letters from baseline at 2 years. Ranibizumab received the FDA approval for all types of neovascular AMD in 2006. Based on the results of these two landmark studies, anti-VEGF therapies for neovascular AMD have largely replaced previous treatment modalities.

2. Background

2.1 Overview of the market (unmet needs, competitor compounds/in clinical development)

By far the most commonly used anti-VEGF drugs currently in use for neovascular AMD are ranibizumab and bevacizumab. Pegaptanib was the first anti-VEGF drug approved by the FDA for the treatment of AMD; however, it proved less efficacious than current treatments [13] (possibly due to its selective binding of VEGF-165) and is no longer widely used in most countries. Ranibizumab is the only drug in widespread use currently approved by the FDA for treatment of neovascular AMD and is by far the most extensively studied [26,27,29,30]. It is a recombinant monoclonal antibody fragment with a high binding affinity for all isotypes of VEGF-A. Bevacizumab, currently being used off-label for the treatment of AMD in the US, is a humanized whole antibody to VEGF-A used in oncology regimens that also binds all isotypes of VEGF-A. Although ranibizumab has been shown to have a higher affinity for VEGF-A, it is not clear if ranibizumab has superior efficacy to bevacizumab. Retrospective and small randomized studies have suggested similar efficacy profiles [31,32]. The Comparisons of Age-Related Macular Degeneration Treatment Trial (CATT) is a 2-year, multi-centered, randomized clinical trial comparing ranibizumab and bevacizumab for neovascular AMD. Enrollment began in February 2008. Despite the off-label status of bevacizumab, it continues to be a popular treatment choice in the US because of the significantly reduced price of treatment ($ 50 – 100 for bevacizumab versus $ 2000 for ranibizumab (2008 pricing)).

As previously mentioned, the MARINA [26] and the ANCHOR [27,28] trials examined the efficacy of ranibizumab when administered monthly. The time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules. In the PIER study [30], patients initially received monthly injections of ranibizumab for 3 months followed by quarterly injections. Although patient visual acuities actually improved at 3 months, during the quarterly dosing segment visual acuity returned to baseline. The PrONTO study [29] looked at as needed (p.r.n.) dosing of ranibizumab after three consecutive monthly doses. The need for further injections was made on the basis of recurrent CNV as evidenced by worsening vision, retinal thickening on ocular coherence tomography (OCT) or abnormalities on fluorescein angiogram (FA). At 2 years of follow up, 78% of patients had maintained vision and vision had improved by > 3 lines in 43% of patients with an average of five injections a year. These later studies seem to indicate that quarterly dosing is associated with poorer outcomes but it may be possible to extend the time between injections if the patient is frequently monitored. However, even with the p.r.n. dosing utilized in the PrONTO study, patients are still required to make monthly visits to the office with frequent and expensive testing.

The development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action. Most new compounds in development are targeted toward inhibition of various steps in the VEGF signaling pathway. There are a number of drugs in development that inhibit the downstream tyrosine kinase cascade activated by the binding of VEGF with its receptor (VEGFR). Vatalanib is an oral formulation that binds to all three VEGFRs and has recently completed Phase I/II study as adjuvant to PDT and ranibizumab [33]. Topical tyrosine kinase inhibitors currently undergoing Phase II clinical studies include pazopanib [34] and TG100801 [35]. Another approach utilizes siRNA to silence genes which express proteins involved in angiogenesis. Bevasiranib, an siRNA that targets VEGF-A mRNA, showed encouraging Phase I and II data, but the Phase III trial was halted in March 2009 for projected failure to meet the primary end point [36]. An extra antiangiogenic target being developed is pigment epithelium-derived factor (PEDF), a potent inhibitor of new vessel growth. AdGVPEDF.11D uses an adenovector to deliver the PEDF gene to target cells, resulting in the local production of PEDF in the treated eye. AdGVPEDF.11D has recently completed Phase I clinical trials [37]. Another

recently discovered alternative pathway for decreasing angiogenesis involves inhibition of nicotinic acetylcholine receptors. ATG3 (mecamylamine), a topical formulation that inhibits the nicotinic acetylcholine receptors, has shown promising results in animal and Phase I trials and is currently undergoing a Phase II study [25].

2.2 Introduction to compound

VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA) in the US and in collaboration with Bayer HealthCare (Leverkusen, Germany) in global markets. Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Figure 1). Functionally, VEGF Trap-Eye acts as a receptor decoy with high affinity for all VEGF isoforms, binding more tightly than their native receptors. Unlike anti-VEGF drugs currently in use, VEGF Trap-Eye is designed to inhibit placental growth factors-1 and -2 in addition to all isoforms of VEGF-A.

2.3 Chemistry

VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations. Both aflibercept and VEGF Trap-Eye are manufactured in bioreactors from industry standard Chinese hamster ovary cells that overexpress the fusion protein. However, VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye. VEGF Trap-Eye is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.

2.4 Pharmacodynamics

The aflibercept dose that is administered in oncology settings is either 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks, which corresponds to 2 mg/(kg week) with either schedule. The highest intravitreal dose being used in pivotal trials for VEGF Trap-Eye is 2 mg/month, which corresponds to at least a 280-fold lower potential systemic exposure than in the oncology setting. Early trials with aflibercept administered intravenously for AMD indicated that doses of 0.3 mg/kg (21 mg total) were inadequate to fully capture systemic VEGF. Thus, the low intravitreal dose of 2 mg allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated.

2.5 Pharmacokinetics and metabolism

Aflibercept is cleared from circulation through two pathways: by binding to VEGF to form an inactive VEGF–aflibercept complex and by Fc-receptor or pinocytotic mediated pathways that end in proteolysis, which are presumed to be similar to pathways that metabolize antibodies. At very high doses, free aflibercept has a terminal half-life of ~ 17 days in the circulation. The half-life of human intravitreal doses is unknown. Intravitreal primate doses of ranibizumab have a half-life of ~ 3 days [38]. At low blood levels, clearance of free aflibercept is rapid as a result of binding to VEGF with picomolar affinity [39].

2.6 Clinical efficacy

2.6.1 *Phase I*

A Phase I, randomized, double-blind, placebo-controlled trial of intravenous aflibercept (oncology formulation) was completed in 25 patients with AMD. Although systemic aflibercept did demonstrate a dose-dependent decrease in retinal thickness, the study was halted due to concerns of dose-dependent toxicity when one patient developed hypertension and another proteinuria [40].

The safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two-part Clinical Evaluation of Anti-angiogenesis in the Retina-1 (CLEAR-IT-1) study [41]. The first part was a sequential cohort dose-escalation study in which 21 patients were monitored for safety, changes in foveal thickness on OCT, best corrected visual acuity (BCVA) and lesion size on FA for 6 weeks. No adverse systemic or ocular events were noted and visual acuity remained stable or improved ≥ 3 lines in 95% of patients with a mean increase in BCVA of 4.6 letters at 6 weeks [42]. Patients showed substantially decreased foveal thickness [41].

In the second part, 30 patients received a single intravitreal injection of either 0.5 or 4 mg of VEGF Trap-Eye and were followed for 8 weeks. All patients were evaluated for their rates of retreatment, changes in BCVA, foveal thickness as well as change in total lesion size and area of CNV. Patients had ETDRS (Early Treatment of Diabetic Retinopathy Study) BCVA ranging from 20/40 to 20/320 with any angiographic subtype of CNV at baseline. No serious adverse events or ocular inflammation was identified during the study. At 8 weeks, the mean decrease in retinal thickness in the low dose group was 63.7 µm compared to 175 µm for the high dose group. Of the first 24 patients to complete the study, 11 out of 12 patients in the 0.5 mg dose group required retreatment in a median of 64 days, compared with 4 out of 12 in the 4 mg dose group who required retreatment in a median of 69 days [43].

VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of diabetic macular edema (DME) [44]. The drug was administered as a single 4 mg intravitreal injection to five patients with longstanding diabetes and several previous treatments for DME. The single injection resulted in a median decrease of central macular thickness measured by OCT of 79 µm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks.

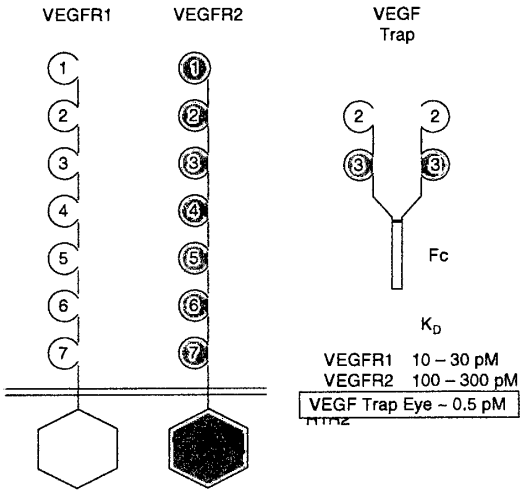

Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

2.6.2 *Phase II*

CLEAR-IT-2 trial [45] was a prospective, randomized, multi-center, controlled dose- and interval-ranging Phase II trial in which 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. The mean age of the group was 78.2 years and all angiographic subtypes of CNV were represented at baseline. The mean ETDRS BCVA in letters at baseline was 56. Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) and three groups received quarterly doses of either 0.5, 2.0 or 4.0 mg for 12 weeks (at weeks 0 and 12). Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness of ≥ 100 µm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks. During the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections. The median time to first reinjection in all groups was 110 days and 19% of patients required no more injections at week 52. Patients in these two monthly dosing groups also displayed mean decreases in retinal thickness versus baseline of 143 µm ($p < 0.0001$) in the 2.0 mg group and 125 µm ($p < 0.0001$) in the 0.5 mg group at 52 weeks as measured by OCT [45].

Patients in the three quarterly dosing groups also showed mean improvements in BCVA and retinal thickness; however, they were generally not as profound as the monthly injection group [45].

2.6.3 *Phase III*

A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

2.7 Safety and tolerability

Based on Phase II study data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events. In the 157 patients enrolled in CLEAR-IT 2 trial, there was one reported case of culture-negative endophthalmitis not deemed to be related to the study drug. There were also two deaths (one from pre-existing pulmonary hypertension and one from pancreatic carcinoma) and one arterial thromboembolic event (in a patient with a history of previous stroke) that occurred during the study period, but no serious systemic adverse events were deemed related to VEGF Trap-Eye administration. The most common adverse events reported in the study included conjunctival hemorrhage (38.2%), transient increased intraocular pressure (18.5%), refraction disorder (15.9%), retinal hemorrhage (14.6%), subjective visual acuity loss (13.4%), vitreous detachment (11.5%) and eye pain (9.6%) [45].

3. Conclusion

Anti-VEGF therapy has vastly improved the treatment of neovascular AMD in terms of both safety and efficacy. The ANCHOR [26] and MARINA [27,28] trials have established ranibizumab as an effective therapy when dosed monthly. It has been shown to stabilize vision in 94% of patients and in almost 40% of patients vision will actually improve by 3 or more lines. However, the monthly dosing schedules used in these trials present a financial and time burden to patients and healthcare practitioners. The more recent PIER [30] and

PrONTO [29] trials have shown that ranibizumab is less effective when dosed quarterly, but it may be possible to extend the time between injections when patients are followed closely with frequent examinations and ancillary testing. The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established but new treatments are aimed at extending and improving on the efficacy of ranibizumab. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-1 and -2. Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD. In Phase II study data, patients dosed in a similar fashion to the PrONTO trial demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year. Of the greatest interest, patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase. While this number is difficult to compare directly to the number of injections required during the p.r.n. phase of the PrONTO ranibizumab study, it is promising. A direct comparison of the efficacy of VEGF Trap-Eye versus ranibizumab will be possible with the completion of two Phase III trials, the VIEW-1 and -2 studies.

4. Expert opinion

The advent of anti-VEGF therapy for treatment of neovascular AMD has revolutionized therapy for a common blinding disease. Before the development of pegaptanib, ranibizumab and bevacizumab, the diagnosis of neovascular AMD portended a prognosis of nearly universal decline in vision, and frequently loss of useful vision in the affected eye.

Current treatment regimens with either ranibizumab or bevacizumab now afford stabilization of vision in > 90% of patients, with significant vision gain in one-third of all patients treated. There have been no significant, proven adverse systemic effects with the intraocular use of either drug. However, limitations of current therapy include the need for frequent intraocular injections, as often as monthly, without a defined stopping point. Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients during their treatment course.

Desirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals. For other indications, time-release delivery methods have met with some success, including the following agents: intraocular steroids, including polymeric fluocinolone and dexamethasone, lasting 3 years and 6 months, respectively [48-50], and for a single biologically active cytokine, ciliary neurotrophic factor, which is released for a period greater than 1 year by encapsulated, bioengineered, implanted cells [51]. While efforts are underway to develop encapsulated cell technology for sustained-release anti-VEGF therapy, no investigational drugs or devices have progressed yet to clinical trial enrollment.

VEGF Trap-Eye represents the most promising anti-VEGF investigational drug that is currently in Phase III trial. VEGF Trap-Eye, a decoy VEGF receptor protein, binds all isoforms of free VEGF with high affinity, in addition to placental growth factor. In contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF–VEGF Trap complex is relatively inert, and is degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.

Data from the Phase II study with VEGF Trap-Eye were positive and the results from the non-inferiority Phase III trials will establish its efficacy versus ranibizumab. Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals. If effective at 4 week intervals only, VEGF Trap-Eye will be adopted into clinical practice if it offers a competitive price advantage over ranibizumab. If effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, and would probably find wide acceptance. The second p.r.n. dosing stage of the Phase III trial will also provide insight into whether VEGF Trap-Eye offers longer duration of treatment effectiveness than ranibizumab.

Data from the VIEW-1 and VIEW-2 trials will need to be interpreted by clinicians in the context of emerging adjuvant therapies that may extend the time between anti-VEGF therapy injections. Many clinicians now treat patients with anti-VEGF therapies in combination with verteporfin PDT. Randomized, open-label studies and one large retrospective case series database seem to indicate lower retreatment rates and improved visual outcomes when compared with monotherapy [52-55]. As a result, at least two prospective, randomized trials are currently underway to further examine combination verteporfin PDT and anti-VEGF treatments [56,57]. An extra combination treatment currently under study is the use of epiretinal brachytherapy with Strontium-90 combined with bevacizumab. A recently published small pilot study showed good safety and efficacy with a single application of epiretinal radiation and two bevacizumab injections after 12 months [58]. A larger, multi-center Phase III trial is underway [59].

Anti-VEGF agents are currently only approved for the treatment of exudative AMD. The multifactorial nature of DME, including non-VEGF mediated causes such as pericyte and endothelial cell damage and tractional mechanisms, has made treatment of this condition difficult using current modalities. Clinical studies are underway with anti-VEGF agents in DME and retinal vein occlusion. VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion. The

FDA approval of VEGF Trap-Eye for these indications would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease.

Eventually, injectable agents targeting the VEGF pathway may be supplanted by implantable devices that deliver polymer-bound drug or manufacture the protein *in vivo*. Further therapies for neovascular AMD such as targeted radiation may confer extra treatment benefit. In the meantime, VEGF Trap-Eye is a promising investigational drug that, if approved, will improve ophthalmologists' ability to treat neovascular AMD.

Declaration of interest

SCN Oliver is a clinical investigator for Genentech and Alcon. JL Olson and N Mandava are clinical investigators for Genentech, Regeneron and Alcon.

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OBS6

REVIEW ARTICLE

Advances in the Medical Treatment of Diabetic Retinopathy

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Proliferative diabetic retinopathy (PDR) remains the leading cause of blindness among working-age individuals in developed countries (1). Diabetic macular edema (DME), another important event that occurs in diabetic retinopathy, is more frequent in type 2 than type 1 diabetes (2). Whereas PDR is the most common sight-threatening lesion in type 1 diabetes, DME is the primary cause of poor visual acuity in type 2 diabetes. Because of the high prevalence of type 2 diabetes, DME is the main cause of visual impairment for diabetic patients (2). In addition, DME is almost invariably present when PDR is detected in type 2 diabetes (3). Neovascularization caused by severe hypoxia is the hallmark of PDR, whereas vascular leakage caused by the breakdown of the blood retinal barrier (BRB) is the main event involved in the pathogenesis of DME (4,5).

STANDARD TREATMENT— Although tight control of both blood glucose levels and hypertension is essential to prevent or arrest progression of the disease, the recommended goals are difficult to achieve in many patients and, consequently, diabetic retinopathy develops during the evolution of the disease. When PDR or clinically significant DME do appear, argon-laser photocoagulation is currently indicated, which the efficacy of has been widely demonstrated (6). However, the optimal period for laser treatment has frequently passed; moreover, it is not uniformly successful in halting visual decline. In addition, argon-laser photocoagulation is associated with moderate visual loss, some diminished visual field, reduced color vision, and reduced contrast sensitivity. The presence of these symptoms led to the prevailing thinking that laser treatment prevents vision loss but rarely results in visual improvement.

Intravitreal corticosteroids have been successfully used in the eyes of patients with persistent DME and loss of vision following the failure of conventional treatment (i.e., focal laser treatment and attention to systemic risk factors). However, reinjections are commonly needed, and there are substantial adverse effects such as infection, glaucoma, and cataract formation (6). In addition, recent reports have shown that focal/grid photocoagulation is more effective and has fewer side effects than intravitreal triamcinolone for DME (7,8).

Vitreoretinal surgery is an expensive and complicated treatment that should be carried out only by vitreoretinal specialists experienced in this procedure, and it is normally reserved for the ultimately blinding complications of PDR, such as severe vitreous hemorrhage and secondary retinal detachment. For these reasons, new pharmacological treatments based on the understanding of the pathophysiological mechanisms of diabetic retinopathy are needed.

The paucity of relevant clinical studies addressed to testing new drugs in diabetic retinopathy is due, in part, to the necessity of long-term studies performed in large cohorts of diabetic patients by means of standardized masked grading of retinal photographs. Although there is no fixed rule, the duration of the trial must be consistent with the natural history of diabetic retinopathy and, consequently, at least 5 years seems to be necessary for separating the behavior of retinopathy in the intervention and control groups. In addition, most clinical trials have been aimed at evaluating the progression of diabetic retinopathy, whereas there have been few studies targeting prevention. All these caveats should be kept in mind when analyzing clinical trials on diabetic retinopathy because they can significantly contribute to false-negative results. The presence of diabetic retinopathy in nondiabetic subjects is another challenge. Wong et al. (9), in a study that included more than 11,000 participants from three population cohorts, provide evidence that with the current fasting plasma glucose cutoff of 7.0 mmol/l used to diagnose diabetes, 7.4–13.4% of nondiabetic patients had diabetic retinopathy. This finding, apart from questioning the current diagnostic criteria of diabetes, suggests a potential limit to the risk reduction for diabetic retinopathy that should be taken into consideration when interpreting the results of clinical trials.

Recently, two pivotal studies have been published regarding the beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy (10–12). These studies fulfill all the main requirements for obtaining a valid result: long-term follow-up (~5 years), a large cohort of diabetic patients, retinopathy assessed by standardized methods, and a significant number of patients without diabetic retinopathy at study entry, thus allowing evaluation of the effectiveness of prevention. In advanced stages of diabetic retinopathy, intravitreous anti–vascular endothelial growth factor (VEGF) agents have emerged as new treatments. These drugs are yet to be approved for diabetic retinopathy treatment, but they are currently used by ophthalmologists in selected cases of PDR and DME (13,14). This article discusses the current state of knowledge concerning these novelties in the medical treatment of diabetic retinopathy and highlight areas where further studies and evidence are required.

FENOFIBRATE— Fenofibrate is a peroxisome proliferactor–activated receptor (PPAR)-α agonist indicated for the treatment of hypertriglyceridemia and mixed dislipidemia. Its main action is to lower plasma triglyceride levels, but it also reduces total and LDL cholesterol, raises HDL cholesterol, and decreases

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concentration of small LDL cholesterol particles and apolipoprotein B (15). Recently, Keech et al. (10) have reported results concerning laser treatment for diabetic retinopathy from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. The main aim of this randomized controlled trial was to assess whether long-term lipid-lowering therapy using fenofibrate (a PPAR-α agonist) could reduce the need for laser treatment in a large cohort (n = 9,795) of type 2 diabetic patients. The average follow-up was 5 years, and the end point was the need for laser treatment (a tertiary end point of the main study). In an intention-to-treat analysis, fenofibrate (200 mg once daily) reduced the frequency of laser treatment for macular edema by 31% and for proliferative retinopathy by 30%. In addition, in a substudy performed on patients in whom retinal status was graded by fundus photography, fenofibrate was able to reduce the progression of existing retinopathy. Although this study has some limiting factors (16,17), the substantial benefits obtained from reducing the need for laser treatment argue for consideration of using fenofibrate in the management of diabetic retinopathy. However, our poor knowledge of the mechanisms involved in its beneficial effects in diabetic retinopathy might limit its potential impact on clinical practice. Theoretically, another PPAR-α apart from fenofibrate can also be beneficial for diabetic retinopathy; however, at present this has been only demonstrated with fenofibrate.

The rationale for FIELD was that elevated lipid levels in systemic circulation constitute a risk factor for diabetic retinopathy; therefore, long-term lipid-lowering therapy with fenofibrate could reduce the progression of diabetic retinopathy and the need for laser treatment in patients with type 2 diabetes. However, no relationship between serum lipids and the appearance or progression of diabetic retinopathy was detected. This is in agreement with other prospective studies showing that serum lipids are unrelated to the progression of diabetic retinopathy or the development of PDR (18,19). In addition, the Collaborative Atorvastatin Diabetes Study (CARDS), a randomized controlled trial of 2,830 patients with type 2 diabetes, did not find atorvastatin to be effective in reducing diabetic retinopathy progression (20). However, this study was limited by substantial missing data (only 65% of patients had retinopathy status recorded at baseline) and lack of photographic grading for diabetic retinopathy. Another randomized trial, the ACCORD-EYE study that is now in progress, could shed light on this issue (21). In this study, the effects of lipid control (statin vs. fenofibrate added to a statin) on the progression of diabetic retinopathy will be evaluated. There will be 4,065 participants recruited to the study at baseline for whom fundus photographs will be taken within 4 months of randomization and again 4 years later. Although in the FIELD study there was no relationship between the quantitative levels of serum lipids and diabetic retinopathy, it is unknown whether the effectiveness of fenofibrate in modulating the qualitative properties of lipoproteins (i.e., reducing remnants and small dense LDL particles) can contribute to its beneficial effects. In addition, it should be noted that the mechanisms regulating intraretinal lipid transport rather than serum levels might be more important in the pathogenesis of diabetic retinopathy. In this regard, we have recently shown that apolipoprotein A1 (apo-A1) is overexpressed in the retina of diabetic patients (22). Apo-A1 is a key factor for the intraretinal transport of lipids, thus preventing lipid deposition and lipotoxicity, and it is also a potent scavenger of reactive oxygen species. Therefore, apo-A1 could play an important role in protecting the retina from oxidative stress. These findings have led us to hypothesize that the retinas from diabetic patients have a higher content of apo-A1 as a protective mechanism; consequently, patients with less capacity for apo-A1 production by the retina will be more prone to develop lipid deposition (hard exudates) and retinal damage induced by oxidative stress. Fenofibric acid was shown to enhance transcription of the gene of apo-A1 in the liver (23), macrophages, and fibroblasts (24), but whether this is also true at the retinal level remains to be elucidated.

Other nonlipidic mechanisms by which fenofibrate could be effective in preventing or arresting diabetic retinopathy might be the following:

1) PPAR-α is present in endothelial cells (25), and its activation by means of PPAR-α agonists has recently been shown to inhibit expression of VEGF receptor 2 (VEGFR2) and neovascularization in human umbilical endothelial cells (26). Varet et al. (27) have demonstrated that fenofibrate inhibits angiogenesis in vitro and in vivo as well as basic fibroblast growth factor–induced angiogenesis in vivo. In addition, in cells derived from human ovarian cancer, clofibric acid (a PPAR-α agonist) downregulates VEGF expression (28). Apart from its antiproliferative effects, fenofibrate inhibits the apoptosis induced by high glucose concentrations in human umbilical endothelial cells (29). Moreover, it has been demonstrated that fenofibrate prevents the apoptosis of human retinal endothelial cells induced by serum deprivation through a PPAR-α–independent but AMP-activated protein kinase–dependent pathway (30). This activation of the AMP-activated protein kinase pathway in endothelial cells could lead to an increase in endothelial nitric oxide synthase phosphorylation and nitric oxide production, thus resulting in beneficial effects on endothelial function (31).
2) PPAR-α is associated with anti-inflammatory and antioxidant activity (32). It has been reported that PPAR-α activation induces the expression and activation of antioxidant enzymes, such as superoxide dismutase and glutation peroxidase (33), and that activation of PPAR-α induces apoptosis of human monocyte–derived macrophages (34). In addition, PPAR-α activators inhibit the expression of vascular cell adhesion molecules on the endothelium (35). This effect might be useful in preventing leukostasis (the inappropriate adherence of leukocytes to the endothelium), which is essential in the pathogenesis of PDR.
3) PPAR-α activation also has a neuroprotective effect (33,36). This could be important in preventing neuroretinal degeneration, an early and crucial event that occurs in diabetic retinopathy even before vascular abnormalities can be detected (37).
4) The breakdown of the BRB, caused by the disruption of tight junctions and subsequent leakage, is the main factor accounting for DME (6). Because of the notable effect of fenofibrate in preventing DME progression, it would be worthwhile to explore whether fenofibrate is able to reduce the increased permeability that exists in diabetic retinopathy.

Future research on the potential effects of fenofibrate in all these areas will be essential for understanding its beneficial effects in diabetic retinopathy, and it will also be critical for using this drug as an adjunct in the management of diabetic retinopathy.

BLOCKING THE RENIN-ANGIOTENSIN SYSTEM — Observational and clinical trials have shown that blood pressure is an important modifiable risk factor for diabetic retinopathy and that lowering high blood pressure significantly reduces the development and progression of retinopathy in both type 1 and type 2 diabetic patients (38,39). The blockade of the renin-angiotensin system (RAS) with an ACE inhibitor or by using angiotensin II type 1–receptor (AT1-R) blockers is one of the most used strategies for hypertension treatment in diabetic patients. Apart from the kidney, the RAS system is expressed in the eye (40). In addition, there is growing evidence that RAS activation in the eye plays an important role in the pathogenesis of diabetic retinopathy (40). Therefore, apart from lowering blood pressure, the blockade of the RAS could also be beneficial per se in reducing the development and progression of diabetic retinopathy.

The major components of RAS have been identified in ocular tissues and are overexpressed in the diabetic retina. Angiotensin II (AT) binds and activates two primary receptors, AT1-R and AT2-R. In adult humans, activation of the AT1-R expressed in endothelial cells and pericytes dominates the pathological states (40). AT1-R activation by AT produced by the retina stimulates several pathways involved in the pathogenesis of diabetic retinopathy such as inflammation, oxidative stress, cell proliferation, pericyte migration, remodelling of extracellular matrix by increasing matrix metalloproteinases, angiogenesis, and fibrosis (40). The RAS is upregulated concomitant with hypoxia-induced retinal angiogenesis and is linked to AT-mediated induction of inflammatory mediators and growth factors, including VEGF and platelet-derived growth factor (40,41). In addition, AT1-R activation by AT promotes leukostasis and neurodegeneration (40), two key elements in the pathogenesis of diabetic retinopathy. Most of these pathogenic actions are inhibited or attenuated by pharmacological blockade of the RAS either at levels of ACE or the AT receptors and are accompanied by downregulation of VEGF and VEGFR-2 (40). Recently, Kim et al. (42) have shown that perindopril (an ACE inhibitor) attenuates VEGF-mediated BRB breakdown in rats with streptozotocin-induced diabetes. In addition, it is also worthy of mention that candesartan inhibited retinal accumulation of the advanced glycation end product pentosidine in spontaneously diabetic Torii rats (43). Apart from reducing microvascular disease, there is growing evidence pointing to neuroprotection as a relevant mechanism involved in the beneficial effects of angiotensin receptor blockers in diabetic retinopathy (44–46).

On these experimental bases, it would be reasonable to postulate that RAS blockade can promote higher beneficial effects in diabetic retinopathy than other antihypertensive agents. However, studies in type 2 diabetic patients with hypertension suggest that ACE inhibitors and angiotensin receptor blockers are not superior in preventing or arresting diabetic retinopathy to other drugs equally effective in reducing blood pressure such as the β-blocker atenolol (47) or calcium channel blocker nisoldipine (48). These prospective randomized studies suggest that lowering blood pressure seems to be much more important than the potential effect of RAS blockade in the diabetic eye. However, the question concerning the potential effect of RAS blockers in normotensive diabetic patients remains to be elucidated. In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID), it was reported that in normotensive patients (blood pressure ≤140/90 mmHg), either normoalbuminutic (85% of patients) or microalbuminuric, lisinopril (an ACE inhibitor) had no effect in reducing the incidence of diabetic retinopathy but decreased its progression by two or more grades and decreased the progression to PDR (49). However, these results have been criticized because the placebo group had significantly higher levels of mean A1C than the treatment group. In fact, after adjusting for A1C, the observed differences in progression by two levels and progression to PDR disappear and only the progression by one level remained significant. Other limiting factors of this study were the short period of follow-up (2 years) and the fact that diabetic retinopathy was not the primary end point of the study. Therefore, although the EUCLID study supported the idea of an additional benefit of ACE inhibitors on diabetic retinopathy progression, it was underpowered for the eye-related outcome measures used. Furthermore, in the normotensive type 2 diabetic patients of the Appropriate Blood Pressure Control in Diabetes (ABC) study, Schrier et al. (50) showed that intensive blood pressure control decreased the progression of diabetic retinopathy. However, the results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent. Therefore, the specific antihypertensive agent again appears to be less important than the achievement of the lower blood pressure values.

The Diabetic Retinopathy Candesartan Trials (DIRECT) program was therefore designed to answer the question of whether the blockade of RAS with AT1-R blocker candesartan could prevent the incidence and progression of retinopathy in type 1 and type 2 diabetes independent of lowering blood pressure (11,12). This program consisted of three randomized double-blind placebo-controlled parallel-group studies: *1*) a primary prevention study involving 1,241 type 1 diabetic patients without diabetic retinopathy (DIRECT-Prevent 1), 2) a secondary prevention study involving 1,905 type 1 diabetic patients with diabetic retinopathy (DIRECT-Protect 1), and *3*) a secondary prevention study involving 1,905 type 2 diabetic patients with diabetic retinopathy (DIRECT-Protect 2). In each trial, patients were randomized to receive candesartan (16–32 mg/day) or placebo and the median follow-up was 4.7 years. Patients with type 1 diabetes were eligible for inclusion if they were normoalbuminuric and normotensive (blood pressure ≤130/85 mmHg). For patients with type 2 diabetes, the inclusion criteria were normoalbuminuria and either normal blood pressure without antihypertensive therapy or blood pressure ≤160/90 mmHg during treatment. The primary end point was the incidence of diabetic retinopathy in the primary prevention study and progression of diabetic retinopathy in the secondary prevention studies. In the DIRECT-Prevent 1 study, a nonsignificant reduction (18% relative risk reduction; $P = 0.051$) in the risk of incidence of diabetic retinopathy was observed. However, in a post hoc analysis in which the primary end point was changed from a two-step increase to at least a three-step increase in the ETDRS scale, a significant difference was detected (35% relative risk reduction; $P = 0.003$). This beneficial effect was attenuated but still significant af-

ter the data were adjusted for duration of diabetes, A1C, and systolic blood pressure (26% relative risk reduction; $P = 0.046$) (11). In DIRECT-Protect 1, an identical progression of diabetic retinopathy was found in the placebo and in the candesartan groups, thus suggesting that candesartan is not effective in preventing diabetic retinopathy progression (11). DIRECT-Protect 2 showed a nonsignificant reduction in the progression of diabetic retinopathy (13% relative risk; $P = 0.20$). However, a significant increase in diabetic retinopathy regression was observed (34%, $P = 0.009$), this effect being more evident in patients with mild retinopathy (12). Thus, although the prespecified primary end point was not reached in the DIRECT program, data analysis suggests an overall beneficial effect of candesartan in diabetic retinopathy.

The DIRECT results should be compared with the Action in Diabetes and Vascular Disease (ADVANCE) study, which included 11,140 type 2 diabetic patients (51). In this study, patients randomized to intensive glucose control with glicazide (modified release), as well as other drugs required to achieve A1C ≤6.5% and an ACE inhibitor–diuretic combination (perindopril-indapamide), presented the same 4-year incidence or progression of diabetic retinopathy as the placebo group. These results suggest the possibility that candesartan but not ACE inhibitors might have beneficial effects in diabetic retinopathy. However, it should be noted that unlike DIRECT, ADVANCE did not use standardized retinal photography and there was a lower rate of progression of diabetic retinopathy, thus limiting the power of the study to detect any moderate effects of intervention on microvascular eye disease.

INTRAVITREAL ANTI-VEGF AGENTS— VEGF has been identified as having a major role in the genesis of diabetic retinopathy, with increased levels in animals with experimental diabetes and in the vitreous of patients with diabetic retinopathy. Intravitreal VEGF administration in experimental animals duplicates many features of diabetic retinopathy. Thus, agents that attenuate VEGF action are very attractive because they are able to reduce permeability and neovascularization, the hallmarks of DME and PDR, respectively (4,52).

In general, systemically administered drugs reach the retinochoroidal tissue via blood circulation. However, because the BRB limits the influx of drugs into the retina, large amounts of the drug must be administered to maintain therapeutic concentrations. Regarding anti-VEGF agents, this would lead to systemic inhibition of angiogenesis, which could compromise critical vascular response to ischemic events in diabetic patients with cardiovascular, cerebrovascular, or peripheral vascular disease. Moreover, hypertension and proteinuria (two surrogate markers of systemic VEGF inhibition) as well as the impairment of wound healing are other potential consequences of blocking VEGF and would be particularly worrying to the diabetic population (14). By contrast, the local administration of anti-VEGF agents into the eye by means of intravitreal injections would avoid systemic adverse effects. However, this is invasive and a skilled specialist is required. In addition, in order to maintain effective levels, frequently repeated injections would be necessary, thus increasing local complications such as endophthalmitis, vitreous hemorrhage, retinal detachment, and traumatic cataract. Furthermore, although the eye is thought of as a closed and self-contained system, anti-VEGF drugs injected into the vitreous cavity pass into systemic circulation to varying degrees and could potentially cause the systemic adverse effects mentioned previously (14,52). At present four anti-VEGF agents are available: pegaptamib sodium (macugen; Pfizer), ranibizumab (lucentis; Genentech/Novartis), bevacizumab (avastin; Genentech), and aflibercept (Regeneron Pharmaceuticals/sanofi-aventis).

Pegaptanib is a PEGylated (i.e., conjugated to polyethylene glycol) neutralizing RNA aptamer with an extremely high affinity for isoform 165 of VEGF ($VEGF_{165}$), which is the isoform that participates in pathological but not physiological neovascularization (53). Aptamers are modified nucleotides composed of single-stranded nucleic acids that adopt a specific three-dimensional conformation, allowing them to bind with high specificity and affinity to molecular targets in a manner similar to that of monoclonal antibodies. An important feature of aptamers is that they do not exhibit immunogenicity. Pegaptamib was approved by the U.S. Food and Drug Administration (FDA) for treatment of exudative (wet or neovascular) age-related macular disease (AMD) in December 2004.

Ranibimizumab is a full-length monoclonal antibody directed against VEGF. In contrast to pegaptamib, ranimizumab inhibits the biological activity of all isoforms of human VEGF and could be immunogenic. The FDA approved ranibizumab for wet AMD in June 2006.

Bevacizumab is an anti-VEGF agent similar to ranibizumab and was approved by the FDA in February 2004 for the treatment of disseminated colorectal cancer but not licensed for intraocular use. Nevertheless, intravitreal injection of bevacizumab has become a current off-label treatment by ophthalmologists for neovascular AMD because although it seems to be as effective as pegaptamib or ranimizumab, it is much cheaper.

Aflibercept, also known as a VEGF Trap-Eye because of its ability to block all six VEGF proteins (VEGF-A to VEGF-B as well as placental growth factor), is a fusion protein comprised of segments of the extracellular domains of human VEGF receptors 1 (VEGFR1) and 2 (VEGFR2) fused to the constant region (Fc) of human IgG. Aflibercept is currently being used in clinical trials for both exudative AMD and DME. Aflibercept has a higher binding affinity than other anti-VEGF agents. This higher binding affinity translates into greater activity at lower biological levels and, consequently, a longer duration of action.

The results of prospective clinical trials using pegaptanib and ranibizumab in patients with AMD have been very impressive and have led to the design of specific trials for DME and PDR. At present, only a prospective double-blind multicenter dose-ranging controlled trial has been reported in diabetic patients (54). In this study 172 patients with DME were included, and the patients randomized to receive repeated intravitreal pegaptamib showed better visual outcomes ($P = 0.03$), were more likely to show a reduction in retinal thickness ($P = 0.02$), and needed less additional focal laser ($P = 0.04$) at follow-up (36 weeks) than patients who received intravitreal sham injections. Retrospective data analysis of the eyes of 16 patients with PDR also showed regression of neovascularization (55).

Uncontrolled studies using ranibizumab and bevacizumab have also found a rapid regression of retinal neovascularization, improvement of visual acuity, and decrease of retinal thickness in DME, even in nonresponders to conventional treatment (14,56). However, the response to treatment of DME by VEGF blockade is

not prolonged and is subject to significant variability. This is in distinct contrast to the rapid response of those with both iris and retinal neovascularization in PDR and of those with choroidal neovascularization in wet AMD (57). Interestingly, when the outcomes of intravitreal bevacizumab treatment of DME were compared with those of intravitreal cortisone (triamcinolone acetonide), better outcomes in terms of reduction of foveal thickness and visual results were found with triamcinolone (58). The extent to which VEGF blockade is beneficial for DME is currently being investigated in prospective clinical trials. Apart from their potential as isolated treatments for PDR and DME, intravitreal anti-VEGF agents, in particular bevacizumab, have been shown to be useful in increasing the short-term response to panretinal photocoagulation in high-risk PDR and also seem to be efficacious and safe as an adjuvant treatment to vitrectomy in severe PDR or vitreous hemorrhage (56). This is because intravitreal anti-VEGF agents reduce active neovascularization and vitreous hemorrhage, thus allowing a safe and efficient panretinal photocoagulation or pars plana vitrectomy to be performed while minimizing the risk of complications. Aflibercept has been recently tested in an exploratory study performed in five patients with DME (59). In this study, using a single intravitreal injection, Trap-Eye was well tolerated and preliminary evidence of bioactivity was detected. Taken together, these promising results present a new scenario in the management of diabetic retinopathy. Nevertheless, larger studies investigating not only the effectiveness but also the systemic adverse effects of these agents in the diabetic population are still needed.

It is possible that a drug with more extensive and nonspecific anti-VEGF activity, such as pan-VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept), could be more effective than a drug such as pegaptamib that selectively targets $VEGF_{165}$. In this regard, pegaptamib is substantially less effective than ranibizumab in AMD treatment. By contrast, given that $VEGF_{165}$ plays an essential role in pathological but not physiological neovascularization, pegaptanib could be the best option for avoiding systemic adverse effects in diabetic patients. In addition, long-term intravitreous injections of pan-VEGF inhibitors could lead to retinal neurodegeneration and an increased risk of circulation disturbances in the choriocapillaris (60). However, the theoretical advantage of selective blocking of $VEGF_{165}$ by pegaptamib in terms of both systemic and local side effects remains to be demonstrated in head-to-head clinical trials.

CONCLUDING REMARKS AND FUTURE RESEARCH — Tight control of blood glucose levels and hypertension remains the key element for preventing or arresting diabetic retinopathy. However, two drugs (fenofibrate and candesartan), originally not designed for treatment of diabetic retinopathy, have become new adjuncts in its management. The information drawn from clinical trials indicates that in normotensive diabetic patients, candesartan reduces the incidence of diabetic retinopathy in those with type 1 diabetes and favors diabetic retinopathy regression only in type 2 diabetic patients with mild retinopathy. By contrast, fenofibrate, which has only been tested in type 2 diabetes, has no effect on the incidence of diabetic retinopathy. However, it reduces the progression of existing diabetic retinopathy, thus lessening the need for laser treatment in both DME and PDR, and this beneficial effect is unrelated to changes in serum lipids. Therefore, it would be reasonable to recommend candesartan for type 1 diabetic patients (with or without hypertension) at high risk to develop diabetic retinopathy and for type 2 diabetic patients with mild retinopathy, whereas fenofibrate seems to be a good option for type 2 diabetic patients (with or without dyslipemia) with a wide range of diabetic retinopathy stages (from mild to severe nonproliferative diabetic retinopathy). In addition, the benefit on diabetic retinopathy shown by fenofibrate and candesartan should be considered an extra value when treating dyslipemia and hypertension in diabetic patients. Nevertheless, the mechanisms by which candesartan and, in particular, fenofibrate exert their reported benefits need to be elucidated before these drugs can be launched (alone or in combination) as new tools in the management of diabetic retinopathy. Another question needing specific research is whether such treatments could be administered topically and directly into the eye in order to increase the benefits in diabetic retinopathy.

In advanced stages of diabetic retinopathy, intravitreal delivery of anti-VEGF agents are currently used by many ophthalmologists despite the lack of phase 3 studies supporting their effectiveness and safety. This is due to the successful results obtained in wet AMD and the promising preliminary data in diabetic retinopathy. Intravitreal injection permits antiangiogenic drugs to effectively reach the retina and theoretically overcomes the problem of the systemic blockade of angiogenesis. However, this is an invasive procedure that can have complications such as endophthalmitis and retinal detachment and could even have deleterious effects for the remaining healthy retina. This is especially important in diabetic patients for whom long-term administration is expected. Apart from local side effects, anti-VEGF agents could also produce systemic complications because of their capacity to pass into systemic circulation. The effectiveness and safety of intravitreal anti-VEGF agents are being evaluated in several clinical trials. Meanwhile, in order to minimize systemic adverse effects, it seems reasonable to avoid long-term treatment with anti-VEGF agents for patients with hypertension, proteinuria, renal failure, cardiovascular disease, and foot lesions with wound healing impairment.

A future scenario will involve using a combination of anti-VEGF agents and laser photocoagulation or combining antiangiogenic agents aimed at different steps of angiogenic cascade. This would probably be more successful than single-molecule–specific approaches, would permit a decrease in the frequency of dosing, and would reduce adverse effects. Although it is premature at this stage to advocate such maneuvers, these aspects are certainly worth pursuing in future studies because they may suggest attractive new strategies for improving the treatment of diabetic retinopathy. However, it should be emphasized that, at present, the milestones in diabetic retinopathy treatment are the optimization of blood glucose levels, lowering of blood pressure, and regular fundoscopic screening.

In summary fenofibrate, candesartan, and anti-VEGF agents are now in the armamentarium for diabetic retinopathy treatment. Ophthalmologists and physicians treating diabetic patients should be aware of the potential usefulness of these drugs and work together not only in future research but also in establishing clinical guidelines that will include these newer medical treatments for diabetic retinopathy. Only such coordinated action, as well as competent strategies targeting prevention, will be effective in reducing

the burden and improving the clinical outcome of this devastating complication of diabetes.

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Current Status of Vascular Endothelial Growth Factor Inhibition in Age-Related Macular Degeneration

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Contents

Abstract

Angiogenesis, the process by which new vessels are created from pre-existing vasculature, has become the subject of intense research in recent years. Increased rates of angiogenesis are associated with several disease states, including cancer, age-related macular degeneration (AMD), psoriasis, rheumatoid arthritis, and diabetic retinopathy. Vascular endothelial growth factor (VEGF) is an important modulator of angiogenesis, and has been implicated in the pathology of a number of conditions, including AMD, diabetic retinopathy, and cancer. AMD is a progressive disease of the macula and the third major cause of blindness worldwide. If not treated appropriately, AMD can progress to involve both eyes. Until recently, the treatment options for AMD have been limited, with photodynamic therapy (PDT) the mainstay of treatment. Although PDT is effective at slowing disease progression, it rarely results in improved vision. Several therapies have been or are now being developed for neovascular AMD, with the goal of inhibiting VEGF. These VEGF inhibitors include the RNA aptamer pegaptanib, partial and full-length antibodies ranibizumab and bevacizumab, the VEGF receptor decoy aflibercept, small interfering RNA-based therapies bevasiranib and AGN 211745, sirolimus, and tyrosine kinase inhibitors, including vatalanib, pazopanib, TG 100801, TG 101095, AG 013958, and AL 39324. At present, established therapies have met with great success in reducing the vision loss associated with neovascular AMD, whereas those still under investigation offer the potential for further advances. In AMD patients, these therapies slow the rate of

vision loss and in some cases increase visual acuity. Although VEGF-inhibitor therapies are a milestone in the treatment of these disease states, several concerns need to be addressed before their impact can be fully realized.

Angiogenesis is a term used to describe the formation of new blood vessels from the pre-existing vasculature. This process is critical for several normal physiologic functions, including the development of embryos, wound healing, the female reproductive cycle, and collateral vascular generation in the myocardium. However, aberrant angiogenesis has been implicated in the progression of several disease states, including cancer, macular degeneration, diabetic retinopathy, rheumatoid arthritis, and psoriasis.

Under normal physiologic conditions, the process of angiogenesis is well controlled, reflecting a perfect balance of endogenous angiogenic growth factors and suppressors. When angiogenic growth factors outnumber angiogenesis inhibitors, the balance shifts in favor of angiogenesis, a process termed the 'angiogenic switch.'[1] Rigorous research in the field of angiogenesis has led to the identification of many regulators involved in this process. Angiogenesis is driven by the production of proangiogenic growth factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-8, placental-like growth factor (PLGF), transforming growth factor-β (TGFβ), nitric oxide synthetase, angiopoietin, platelet-derived growth factor (PDGF), pleiotrophin, and several others.[2] Activation by VEGF and other proangiogenic factors causes endothelial cells to release proteases that degrade the basement membrane. This allows endothelial cells to escape from the original vessel walls, proliferate, and extend toward the source of the angiogenic stimulus, using integrins to mediate cell adhesion.[1,3] Angiogenesis can also be promoted by a deficiency in endogenous angiogenesis inhibitors, which include angiostatin, canstatin, endostatin, various heparinases, interferon-α, -β, -γ, thrombospondin, and others.[3]

The main purpose of this review is to summarize the physiologic role of VEGF, particularly within the eye, and its role in the development of age-related macular degeneration (AMD), and to highlight both the benefits and potential adverse effects of anti-VEGF-based therapy.

1. Pathologic Angiogenesis and Anti-Angiogensis Therapies

Research shows that angiogenesis accompanies the progression of chronic inflammation. VEGF is over-expressed in a number of proinflammatory conditions, including psoriasis and rheumatoid arthritis.[4,5] During tumorigenesis, lack of oxygen and other essential nutrients restricts tumor growth to 1–2 mm.[3,6] In order to grow beyond this size, tumor cells must induce angiogenesis by secreting angiogenic growth factors. This angiogenic vascularization not only allows the tumor to grow, but also increases the rate of metastasis. Vessels formed by uncontrolled and unregulated angiogenesis are drastically different from those of the normal vasculature, being characterized by chaotic branching, hypoxia, and increased interstitial pressure. These irregularities might also hinder the ability of chemotherapeutic agents to reach desired drug concentrations within the tumor vasculature. Thus, VEGF has become an attractive target of investigation for the treatment of various types of cancer.

A wide range of therapies designed to inhibit angiogenesis have been developed and many more are currently under investigation. Angiogenesis inhibitors are typically divided into two categories: direct or indirect. Direct angiogenesis inhibitors are designed to target endothelial cells and prevent their proliferation. Indirect therapies target proangiogenic growth factors or their receptors. In general, endothelial cells are viewed as an excellent target for therapy because they are genetically more stable than cancer cells. In fact, it has been postulated that this stability reduces the likelihood of rapid mutation and acquired drug resistance.[7] Recent studies suggest, however, that tumor endothelial cells carry genetic anomalies that may confer drug resistance.[8,9] Interestingly, it has been suggested that traditional therapies, such as radiation therapy, may actually work in part by targeting genomically stable endothelial cells, as these endothelial cells are still proliferating at a higher than normal rate.[8,9]

Indirect inhibition of angiogenesis can be further divided into two categories, those that amplify the effects of angiogenic inhibitors and activate their associated pathways, or those that inhibit the activation of proangiogenic pathways. Currently, there are a number of angiogenic regulators and their receptors under investigation. For example, a recent phase II trial investigating the use of a TGFβ antisense vaccine, belagenpumatucel-L (Lucanix®), in patients with non-small cell lung cancer reported favorable results.[10] Focusing on 61 assessable patients with late-stage (IIIB and IV) disease, a 15% partial response rate was achieved and the estimated probabilities of

surviving 1 and 2 years were 68% and 52%, respectively. These results were favorable as compared with historic controls, and no significant adverse events were observed. Another promising experimental strategy targeting TGFβ employs the use of a soluble TGFβ receptor, which specifically inhibits TGFβ-1 and TGFβ-3.[11,12]

2. Pathogenesis of Age-Related Macular Degeneration (AMD)

AMD is a multifaceted disease characterized by early subclinical changes at the choroidea-retinal pigment epithelium interface. Both the causal and formal pathogenesis of the disease is still puzzling. The disease can progress into two distinct late forms, 'geographic atrophy' and 'choroidal neovascularization;' the underlying mechanism of this differential progression remains unknown.[13] Late changes are usually responsible for the dramatic loss in central function that has a devastating effect on quality of life. In industrialized countries, the disease is a major cause of visual disability among persons over 60 years of age. Due to demographic right-shift and increased life expectancy, AMD is not only a medical problem, but also has pronounced socio-economic effects. In the last few decades, treatment modalities have been based on the destruction or surgical removal of the neovascular complex. At present, however, the philosophical approach to treatment has changed to one of modifying disease pathology. AMD is a progressive disease that affects the central portion of the retina (the macula). In the earliest stage, deposits called drusen form in the area between the retinal pigment epithelium and the underlying choroid. Advanced AMD, which is responsible for profound vision loss, has two forms: dry and wet. The dry form of advanced AMD results from atrophy of the retinal pigment epithelial layer below the retina. There is currently no treatment option for this type of AMD. In wet AMD (neovascular AMD), neovascularization of the choroid occurs, resulting in blood and protein leakage. The seepage and scarring from these blood vessels eventually cause irreversible damage to the photoreceptors and can lead to vision loss.[13] Angiogenic growth factors, particularly VEGF, have been shown to be elevated in patients with the wet form of AMD and play a key role in the neovascularization process.[14]

Intelligent targeting of the relevant factors and pathways involved in AMD should stop disease progression, reduce complications and improve vision. The first step into this new era has been accomplished with the introduction of anti-angiogenic agents. These new agents act either directly on VEGF or indirectly on the VEGF signaling cascade. It is important to bear in mind, however, that while VEGF contributes at a fundamental level to neovascular processes, it also acts in other physiologic pathways as well.[3]

3. Biologic Activities of VEGF

VEGF belongs to a family of dimeric glycoproteins within the superfamily of PDGFs. While VEGF, also known as VEGF-A, is the most comprehensively studied, other members of this family include VEGF-B, VEGF-C, VEGF-D, and PLGF.[15,16] VEGF-A has several isoforms ($VEGF_{121}$, $VEGF_{121}b$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$) that arise from alternative splicing. Of these isoforms, $VEGF_{145}$ is the most abundant.[17] All VEGF ligands bind to tyrosine kinase receptors, causing the receptors to dimerize and autophosphorylate.[18] Upon binding to its receptor, VEGF initiates a cascade of signaling events that begins with auto-phosphorylation of both receptor kinases, followed by activation of numerous downstream proteins, including phosphoinositide-3-kinase (PI3K), the Ras GTPase activating protein, Ras, mitogen-activated protein kinase (MAPK), and others.[19] VEGF-A binds to VEGF receptor (VEGFR)-1 (also known as fetal liver tyrosine kinase-1, or FLT1) and VEGFR-2 (also known as kinase insert domain receptor [KDR] or FLK1).[18] VEGFR-2 has a higher affinity for VEGF than VEGFR-1, and has been implicated in the potentiation of angiogenesis.[19] The function of VEGFR-1 is less well defined, but seems to include recruitment of monocytes.[19] VEGF-C and VEGF-D bind to a different receptor, VEGFR-3, which has been shown to mediate lymphangiogenesis.[16] VEGF promotes the growth, migration, and proliferation of endothelial cells.[20-22] In addition, VEGF induces vasodilatation and enhances endothelial cell survival.[20,21] These biologic activities occur in few physiologic processes outside wound healing and ovulation, making VEGF an attractive target for therapy.

4. Role of VEGF in AMD

VEGF is over-expressed in patients diagnosed with AMD. In a recent study designed to determine the effect of VEGF over-expression in retinal pigment epithelial cells, investigators injected a recombinant adenovirus vector expressing rat $VEGF_{164}$ into the sub-retinal space of the rat eye.[14] The expression of VEGF messenger RNA (mRNA) was increased in retinal pigment epithelial cells and blood vessels became leaky 10 days post-injection. By 80 days post-injection, new blood

vessels originating from the choriocapillarie were detected, ultimately leading to the formation of choroidal neovascular membranes and death of photoreceptor cells. This study demonstrated that over-expression of VEGF in retinal pigment epithelial cells can induce vascular leakage, new choroidal blood vessel growth, choroidal neovascularization, and neural retina degeneration in the rat eye.[14] This process mirrors the mechanism of vision loss in AMD, supporting the idea that VEGF over-expression plays a key role in AMD.

5. VEGF Inhibition in the Treatment of AMD

Approved therapeutic agents as well as those currently in development that target VEGF employ one of several mechanisms of action to inhibit the VEGF functional pathway. One approach involves the use of monoclonal antibodies (mAbs) to target either VEGF or its receptors. Soluble VEGFRs with high affinity for VEGF have also been designed that prevent VEGF binding to its receptor on endothelial cells. Various small-molecule tyrosine kinase inhibitors (TKIs) have been developed to specifically inhibit VEGFR tyrosine kinase activity. Two unique classes of drugs have emerged that target VEGF mRNA. The first is designed to target post-transcriptional modification of VEGF mRNA and prevent protein translation of VEGF;[23] the second involves the use of small interfering (si)RNA to prevent transcription of VEGF mRNA.[24]

5.1 Aptamer Therapy

Pegaptanib (Macugen®) is approved by the US FDA for the treatment of wet AMD. Pegaptanib is an aptamer, a short RNA oligonucleotide that assumes a specific three-dimensional shape and binds with high affinity to target molecules. Pegaptanib reduces neovascularization by inhibiting a specific isoform of VEGF, $VEGF_{165}$. Efficacy and safety analyses were recently reported in two randomized, sham-controlled, clinical trials.[25,26] The two combined trials, known as the VISION (VEGF Inhibition Study in Ocular Neovascularisation) study, enrolled 1186 patients. Patients received either an intraocular injection of pegaptanib or a similar sham injection every 6 weeks. Visual acuity (VA) was measured using Snellen eye charts, during which patients were asked to identify specific sized letters or lines at a set distance.[25,26]

The VISION study demonstrated a significant difference in loss of VA by 1 year in patients who received pegaptanib as compared with those who received sham injection (a loss of 7.93 letters for pegaptanib vs 15.05 letters for sham; $p < 0.0001$), which was maintained at 2 years.[25,26] The risk of severe loss of VA (loss of 30 letters or more) from baseline was 22% in the sham-injection group and 10% in the pegaptanib group ($p < 0.001$). In addition, patients in the sham group were more likely to lose three or more Snellen lines from their vision as compared with the pegaptanib group at 1 and 2 years ($p < 0.001$ and $p < 0.05$, respectively). These results indicate that pegaptanib is effective in reducing vision loss in patients with several types of AMD.[25,26]

A study on the cost effectiveness of pegaptanib was performed in 2005, from the perspective of the UK government.[26] The results showed that pegaptinib therapy had a mean incremental cost-effectiveness ratio of £8023 per vision year saved, well below the threshold of £20 000 per vision year saved. The therapy was deemed cost effective for the UK government.[26]

5.2 Monoclonal Antibody Therapy

The anti-VEGF mAb ranibizumab (Lucentis®) was approved for the treatment of wet AMD in the US in 2006. In a 2-year, phase III, randomized, double-blind, sham-controlled study, patients received either ranibizumab low dose ($n = 238$), ranibizumab high dose ($n = 240$), or a sham injection administered intravitreally once monthly in one eye for 2 years. The primary outcome of VA was assessed by determining the number of patients who lost fewer than 15 letters from baseline. Compared with the sham-injection group, significantly higher numbers of patients in the ranibizumab groups were more likely to lose fewer than 15 letters (94.5% for high-dose ranibizumab and 94.6% for low-dose ranibizumab vs 62.2% for sham injection; $p < 0.001$).[27] In fact, vision improvement was noted, with mean VA improving by about seven letters in the ranibizumab groups. By comparison, there was a decline of ten letters in the sham-injection group ($p < 0.001$). At the study conclusion, 26.1% and 33.3% of patients in the low- and high-dose ranibizumab groups, respectively, had a VA gain of 15 letters or more, compared with 3.8% of patients in the sham-injection group ($p < 0.001$).[27] These results were similar to and supported earlier phase I/II studies.[28]

Verteporfin photodynamic therapy (PDT) is indicated for wet, neovascular AMD. Prior to the advent of VEGF inhibitors, it was the treatment of choice for wet AMD. Recently, ranibizumab was compared with verteporfin PDT in a 2-year, randomized, double-blind, multicenter trial.[29] Patients received either low- or high-dose ranibizumab or verteporfin PDT. Those patients who received ranibizumab had significantly better VA, as indicated by more patients losing fewer than 15 letters on Snellen charts. Also, more patients in the ranibizumab group

gained 15 or more letters (35.7% in the low-dose and 40.3% in the high-dose ranibizumab groups) as compared with the verteporfin group (5.6%; $p < 0.001$). Severe loss of VA, indicated by a decline of 30 letters or more, occurred in 13.3% of patients receiving verteporfin as compared with none receiving ranibizumab ($p < 0.001$). Two cases of presumed endophthalmitis and one case of serious uveitis were reported in the high-dose ranibizumab group, while no such events occurred in the verteporfin or low-dose ranibizumab groups.[29]

More frequent administration (defined as <2 months mean inter-injection interval) of ranibizumab in the eye resulted in greater gain in VA (+2.3 lines at 6 months) than less frequent injections (+0.46 lines at 6 months; $p = 0.012$).[30] This study found that in a population of patients receiving as-needed injections of ranibizumab for exudative AMD, visual improvement was related to the frequency of injections received, but not to the resolution of fluid on optical coherence tomography. Thus, treatment with ranibizumab on a strictly as-needed basis may result in under-treatment and significantly less gain in VA.[30]

Bevacizumab is closely related to ranibizumab, differing in that it is a full-length humanized mAb against VEGF, whereas ranibizumab is an antigen binding fragment. Currently, bevacizumab is approved by the FDA for first-line treatment of patients with colon cancer, but it is also used on a large scale off-label for the treatment of exudative AMD.[31] An early, non-randomized trial of bevacizumab in patients with wet AMD showed highly significant improvement in vision (mean change in ETDRS [Early Treatment Diabetic Retinopathy Study] letters, + 10) at 4 and 8 weeks following intravitreal injection.[32] Several small, head-to-head, randomized controlled trials subsequently showed that intravitreal administration of bevacizumab was more efficacious than PDT in improving VA,[33-35] and the incidence of adverse effects was low. A recent meta-analysis of the effects of bevacizumab in exudative AMD found that changes in VA associated with bevacizumab were similar to ranibizumb (+5.9–9.8 and +8.6 ETDRS letters, respectively). A major advantage of bevacizumab is cost, which is approximately 1–5% of that associated with ranibizumab.[31] However, large-scale, randomized controlled trials are needed in order to establish the efficacy and safety of bevacizumab.

5.3 Other VEGF-Targeting Approaches in AMD

Several other therapies for AMD that target VEGF are currently being investigated in clinical trials. Aflibercept (VEGF Trap-Eye) is a receptor decoy that targets VEGF with higher affinity than ranibizumab and other currently available anti-VEGF therapies.[36,37] Aflibercept is being studied in phase II trials as an intravitreal injection, as well as in two phase III clinical trials (VIEW-1 and VIEW-2 [VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD]) comparing aflibercept to ranibizumab, which will provide important insight into the clinical applicability of this drug.[37]

Bevasiranib, the first small interfering RNA (siRNA) agent developed for the treatment of neovascular AMD that has shown clinical promise, has an acceptable safety profile supported by preclinical and clinical data.[38] Injected intravitreally, bevasiranib induces catalytic destruction of mRNA to silence gene expression, thereby targeting *de novo* production of VEGF.[38] Bevasiranib does not appear to affect existing VEGF levels, suggesting that there may be a synergistic effect of combining bevasiranib with other anti-VEGF treatments, such as ranibizumab. Other siRNA-based therapies, such as those designed to target VEGFRs (e.g. AGN 211745), are also being investigated. Recently, it was shown that administration of a siRNA targeting hypoxia-inducible factor (HIF)-1α results in marked decreases in VEGF at the mRNA and protein levels within the retinal pigment epithelium.[39] Antagonism of HIF-1α, however, may lead to the over-activation of alternate transcription factors and their respective target genes, leading to less effective inhibition of angiogenesis.[40] siRNA targeting of VEGF, on the other hand, has the advantage of decreasing the production of several clinically important angiogenic factors, thereby more effectively inhibiting angiogenesis.[40] Other potential therapies in development include pigment epithelium-derived factor-based therapies, nicotinic acetylcholine receptor antagonists, integrin antagonists, and sirolimus.

6. Combined Therapies in AMD

Anti-angiogenesis agents have largely supplanted PDT as a first-line therapy for exudative AMD. Clinical studies examining combination treatments in AMD provide strong evidence that PDT in combination with anti-angiogenesis agent(s) may be more effective than monotherapeutic approaches.[41] Available data suggest that PDT can potentially reduce the frequency with which intravitreal injections of anti-angiogenesis agents are required; anti-angiogenesis agents may in turn augment the activity of PDT by inhibiting the counterproductive upregulation of VEGF.[41]

The effect of combined PDT and intravitreal injection of ranibizumab was recently investigated in a pilot study in 28 patients with occult choroidal neo-vascularizaion (CNV) with recent disease progression ($n = 11$) and CNV due to AMD ($n = 17$).[42] An intravitreal injection of ranibizumab was

administered within 12–24 hours after standard PDT, followed by two additional injections of ranibizumab after 1 and 2 months. PDT in combination with intravitreal ranibizumab was well tolerated and effective, with stabilization of VA in 96% of patients. The combination of bevacizumab and low-dose PDT significantly reduced the number of bevacizumab treatments required over 6 months.[43] This particular study was powered to examine number of treatments, but not effects on VA; thus, further studies are required to explore visual outcomes.

A retrospective, case series database study (registry) assessed outcomes for patients with CNV due to AMD treated with verteprofin PDT and bevacizumab.[44] The study included 1196 patients with CNV due to AMD who were treated with one or more combination treatments of intravitreal bevacizumab 1.25 mg administered within 14 days of verteporfin PDT. Combination therapy with PDT and bevacizumab led to vision benefit for most patients, particularly those who were treatment naïve at baseline.[44] The number of re-treatments was lower than published reports with either treatment delivered as monotherapy. Randomized clinical trials are underway to confirm these findings.

Finally, the efficacy and safety of triple therapy consisting of single-session PDT, intravitreal bevacizumab, and intravitreal triamcinolone for the treatment of neovascular AMD was evaluated in patients with subfoveal CNV secondary to AMD.[45] This study concluded that single-session triple therapy might be a useful treatment option for neovascular AMD based on low retreatment rates, sustainable eradication of CNV, and achievement of visual gain. However, the risk and benefits of using intravitreal triamcinolone in addition to combined PDT and intravitreal bevacizumab warrant further evaluation.

7. Comparative Efficacy of Different Therapies in AMD

In a systematic review of pegaptanib and ranibizumab, it was shown that patients with AMD of any lesion type benefited from treatment with either agent on measures of VA as compared to sham and/or PDT treatment.[46] In addition, patients who continued treatment with either drug for up to 2 years appeared to maintain benefits. Cost-effectiveness analysis showed that the two drugs offer additional benefit over the comparators of usual care and PDT, but at increased cost.[46] The relative benefit of each therapy was less clear, due in part to the lack of data from direct comparison head-to-head trials.

The effects of different treatments on serious pigment epithelium detachment (PED) in AMD have been investigated.[47] Therapeutic results were significantly better in patients treated with bevacizumab and ranibizumab than in those treated with pegaptanib, or with a combination of PDT and intravitreal injection of triamcinolone acetonide. Even with treatment, tears of the retinal pigment epithelium or partial flattening of the PED always indicated a worse prognosis in eyes with exudative AMD than in eyes with CNV.[47]

A recent retrospective study compared the safety and efficacy of ranibizumab with bevacizumab in the treatment of patients with neovascular AMD.[48] Bevacizumab or ranibizumab treatment resulted in similar gains in VA and reductions in macular thickness, as documented each month following injection. Thus, intravitreal bevacizumab appears to be as safe and effective as intravitreal ranibizumab in the treatment of exudative AMD.[48] It is likely that a randomized controlled trial, if it can be done, will show that bevacizumab is equivalent to ranibizumab in terms of efficacy and safety.[31] In addition, there are currently no long-term results available to assess whether the effects of these therapies are long-lived or if alternative angiogenesis pathways eventually overcome VEGF inhibition, resulting in disease progression.

8. Anti-VEGF Therapies in Other Indications

Several novel classes of anti-angiogenesis targets are currently under investigation for the treatment of various cancers and deserve mention, as their use could potentially be expanded for ocular indications such as AMD.

8.1 Tyrosine Kinase Inhibition

One of the most intensely investigated therapeutic strategies is the use of inhibitors of the tyrosine kinase cascade downstream of the VEGFR to block the effects of VEGF. Therapies currently in development in this category include vatalanib, TG 100801, pazopanib, AG 013958, and AL 39324.

An oral, multi-targeted receptor TKI, sunitinib (SU11248), inhibits VEGFR-2, PDGF receptor (PDGFR), and FLT3, and has been shown to suppress leakage in an experimental mouse model of CNV caused by AMD.[49] Inhibition of these tyrosine kinase receptors also prevents tumor growth, pathologic angiogenesis, and metastatic progression of certain cancers.[50] In patients with gastrointestinal stromal tumors who had previously not responded to imatinib, sunitinib improved time to progression (TTP) and progression-free survival (PFS) as compared with placebo.[50] Sunitinib is currently approved by the FDA for gastrointestinal stromal tumors.

Sorafenib (Nexavar®, BAY 43-9006) is a TKI that inhibits tumor angiogenesis by blocking the activation of several tyrosine kinase receptors involved in neovascularization and tumor

progression, including VEGFR-2, VEGFR-3, PDGFR-B, FLT3, KIT, and p38-α (MAPK14).[51-53] Sorafenib also inhibits the activities of RAF1 and BRAF, which are involved in the regulation of endothelial apoptosis.[51] In phase III trials, oral sorafenib prolonged PFS as compared to placebo in patients with advanced clear-cell renal-cell carcinoma in whom first-line therapy had failed.[54] In addition, partial responses were significantly higher in the sorafenib group as compared with placebo. Treatment was associated with increased adverse events, including diarrhea, rash, fatigue, hand-foot skin reactions, hypertension, and cardiac ischemia. This study confirmed earlier phase II results showing that sorafenib significantly increased PFS in patients with advanced renal cell carcinoma.[55] Sorafenib is currently FDA approved for liver and renal cancer.

AEE 788 is potent combined inhibitor of epidermal growth factor receptor (EGFR) and VEGFR. *In vitro*, AE 788 effectively inhibits EGFR and VEGFR phosphorylation, exerts anti-proliferative effects in a range of EGFR- and ErbB2 (HER2)-overexpressing cell lines, and inhibits the proliferation of EGF- and VEGF-stimulated human umbilical vein endothelial cells.[56] *In vivo*, AEE 788 decreased tumor growth in several animal models of cancer, including tumors that overexpress EGFR and/or HER2.[56] Oral administration of AEE 788 resulted in high and persistent drug levels in tumor tissue, and inhibited VEGF-induced angiogenesis in a murine implant model.[56] AEE 788 is currently being studied in phase I clinical trials for cancer indications, and represents a potential candidate for ocular trials, pending satisfactory efficacy and safety data.

Axitinib (AG 013736) is an oral selective inhibitor of VEGFR-1, -2, and -3. In a phase II clinical trial of 52 patients diagnosed with metastatic renal-cell cancer who had experienced treatment failure with previous cytokine-based treatment regimes, axitinib was associated with two complete and 21 partial responses, with an objective response rate of 44.2% and a median response duration of 23.0 months.[57] The primary endpoint was objective response (based on RECIST [Response Evaluation Criteria in Solid Tumors]), and secondary endpoints were duration of response, TTP, overall survival, safety, pharmacokinetics, and patient-reported health-related quality of life. Treatment-related adverse events included diarrhea, hypertension, fatigue, nausea, and hoarseness. Overall, the results of this trial indicate that axitinib has clinical activity in patients with cytokine-refractory metastatic renal-cell cancer.

Cediranib (AZD 2171) is a highly potent ATP-competitive inhibitor of recombinant KDR tyrosine kinase activity *in vitro*. AZD 2171 inhibits VEGF-stimulated proliferation and KDR phosphorylation in human umbilical vein endothelial cells, and reduces vessel area, length, and branching in a fibroblast and endothelial cell model of vessel sprouting.[58] *In vivo*, AZD 2171 inhibits the growth of tumor xenografts in various mouse models of carcinogenesis, including colon, lung, prostate, breast, and ovary.[58] The safety and efficacy of AZD 2171 was recently evaluated in a phase I clinical trial in patients with advanced solid tumors.[59]

Vandetanib (Zactima®, ZD 6474) is an orally available inhibitor of VEGFR-2 and EGFR tyrosine kinase activity. In preclinical studies, vandetanib blocked *in vivo* phosphorylation of VEGFR and EGFR, and prevented the growth of transplanted human xenografts in nude mice.[60] However, a phase II trial of vandetanib in patients with previously treated metastatic breast cancer has yielded disappointing results.[61] Forty-six patients were enrolled, and the primary endpoint of objective response was not met (there were no objective responses reported). Diarrhea and rash were reported by 26% of patients; seven patients in the 300 mg cohort had asymptomatic prolongation of the QTc interval. These results indicate that vandetanib monotherapy is generally well tolerated, but has limited efficacy in patients with refractory metastatic breast cancer.

Vatalanib (PTK 787, ZK 222584) is an oral angiogenesis inhibitor that targets all known VEGFRs, including VEGFR-1, -2, and -3, PDGFR, and KIT. The feasibility and safety of PTK 787 in patients with advanced colorectal cancer was demonstrated in a recent phase I study.[62] Expansion of vatalanib in other indications, including AMD, has yet to be explored.

Pazopanib (GW 786034) is a TKI that targets VEGFR-1, -2, and -3, PDGFR, and KIT. A phase I study demonstrated activity in various types of advanced solid tumors.[63] In a phase II trial, pazopanib treatment resulted in stable disease or partial response in 42% (25/60) of patients at 12 weeks.[64] Adverse events included hypertension, fatigue, diarrhea, nausea, and proteinuria. Surprisingly, no cases of hand-and-foot syndrome were reported and only one case of bleeding occurred. Results appear encouraging and phase II/III trials are underway. A placebo-controlled phase III trial is ongoing in patients with untreated or cytokine-treated renal-cell carcinoma.[65]

Tivozanib (AV-951, KRN 951) is an oral TKI specific for VEGFR-1, -2, and -3. Tivozanib potently inhibits VEGF-induced VEGFR-2 phosphorylation in endothelial cells and blocks VEGF-dependent, but not VEGF-independent, activation of MAPKs and subsequent proliferation.[66] Following oral administration to rats, tivozanib decreased microvessel density within tumor xenografts and decreased VEGFR-2 phosphorylation within tumor endothelium.[66] Tivozanib also inhibited tumor growth in a wide variety of human tumor xenograft

models, including lung, breast, colon, ovarian, pancreas, and prostate.[66] A phase I clinical trial of tivozanib involving 40 patients with advanced solid tumors has shown promising results. Notably, of the nine patients in the trial with renal-cell carcinoma, all achieved either a partial response or stable disease, and one patient exhibited a response lasting >30 months.[67] Phase II trials of tivozanib are currently being conducted.

Motesanib (AMG706) is an orally bioavailable inhibitor of VEGFR-1, -2, and -3, PDGFR, and KIT in preclinical models. The drug inhibits human endothelial cell proliferation induced by VEGF, but not by bFGF *in vitro*, and inhibits VEGF-induced vascular permeability in mice.[68] Oral administration of motesanib potently inhibited VEGF-induced angiogenesis in a rat corneal model and induced regression of established A431 xenografts.[68] In a phase I trial enrolling 71 patients with advanced refractory solid tumors, the most frequent adverse events were fatigue, diarrhea, nausea, and hypertension.[69,70] Thirty four (61%) patients had stable disease (at least through 1 month). Motesanib was well tolerated and there was evidence of antitumor activity. Additional studies of motesanib as monotherapy and in combination with various other agents are ongoing.

8.2 Post-Transcriptional Control

PTC 299 is a novel drug that acts to modulate VEGF at the post-transcriptional level by modifying the 5′ and 3′ untranslated regions of VEGF mRNA. Preclinical data has shown that PTC 299 inhibits the production of all isoforms of VEGF and blocks VEGF synthesis in a variety of tumor cell types, including breast, cervical, colorectal, gastric, lung, ovarian, pancreatic, prostate, and renal cancer cells.[23] In animal models, PTC 299 monotherapy reduced the concentrations of VEGF in tumors and plasma, reduced tumor blood vessel density, and inhibited tumor growth.[23] In a phase I study enrolling 52 subjects, interim analysis showed mild adverse events, including headache, dizziness, nausea, vomiting, and stomach discomfort.[25] No bleeding, clotting, hypertension, or proteinuria occurred. Thus, early clinical results indicate that PTC 299 is a promising therapeutic agent, with fewer adverse events than other anti-VEGF therapies.

9. Issues with VEGF Inhibitors

Although VEGF inhibitors represent the culmination of decades of research in the treatment of several disease states, a number of issues need to be addressed before their true benefit can be realized. It is difficult to measure the efficacy of VEGF inhibitors. In cancer, for example, although tumor regression has occurred in some cases, angiogenesis inhibitors are not typically cytotoxic; rather they will more often result in growth stasis. Thus, some of the current criteria used to define whether anti-VEGF therapies are efficacious may need to be modified.

Monoclonal antibodies have historically been considered the 'magic bullet' for therapeutic targeting of cytokines. However, there have been reports of endogenous antibodies that target these therapeutic mAbs, rendering them inactive.[71] One must therefore expect that these types of reactions will occur with anti-VEGF mAbs as well. In addition, pharmacoeconomic analysis is not advanced enough to justify the use of these expensive therapies.

Agents that block VEGF or VEGFRs may very well block or potentiate the effects of other ligands as well. It is difficult to determine what the long-term effects of blocking VEGF and its receptors may be. In clinical trials, a frequent adverse event observed with most VEGF inhibitors is a dramatic increase in the rate of thromboembolic events.[72] Additional studies are needed to inform the determination by practitioners of which patient populations are at risk for an adverse event so as to tailor therapy accordingly.

Common adverse effects of pegaptanib or ranibizumab injections include changes in vision or difficulties seeing, inflammation of different parts of the eye, increased pressure inside the eye, and increased sensitivity to light.[27] Ranibizumab may raise the risk of stroke in elderly people, especially if they have already had a stroke. In addition, many adverse effects may be caused by the actual injection procedure, rather than the drug itself, For example, the injections have been shown to carry a risk of infection.[27]

10. Beyond VEGF-Targeted Therapies

VEGF inhibitors are a milestone in drug development. Despite this, several issues (as mentioned above) make it unlikely that they will be useful in all patients. Again using the example of cancer, VEGF inhibitors appear to be valuable in many types of cancer, but not in all types, and trials using VEGF inhibitors either alone or in combination with chemotherapy have produced mixed results. Thus, it will be helpful to have diagnostic testing available to determine which patients would benefit from therapy. Ideally, patient populations would be identified that could benefit most by targeting a specific angiogenic growth factor or by treatment with a specific class of drug. More data are also needed on potential antagonism/synergy between certain agents in order to predict the most efficacious combinations, thereby enabling practitioners to overcome redundancies that are built into the angiogenic process. Emerging therapies that target different points in the angiogenic process

Table I. Current and investigational anti-vascular endothelial growth factor targets for age-related macular degeneration

Compound	Status
Pegaptanib (Macugen®)	US FDA approved
Ranibizumab (Lucentis®)	US FDA approved
Bevacizumab (Avastin®)	US FDA approved
Aflibercept (VEGF Trap)	Phase III
Sunitinib (Sutent®)	US FDA approved
Sorafenib (Nexavar®)	US FDA approved
Vatalanib (PTK 787, ZK 222584)	Phase II (discontinued)
Pazopanib (GW 786034)	Phase II
Motesanib (AMG 706)	Phase III

may potentially have fewer adverse effects and benefit certain patient populations that cannot be treated with anti-VEGF therapies. Table I lists ongoing trials of agents that target different mechanisms and regulators of angiogenesis.

10.1 Alternative Therapies in AMD

Anecortave acetate (Retaane®) is an angiostatic cortisene that has been shown to be effective in the treatment of AMD.[73] In an uncontrolled clinical series of 19 patients (8 male, 11 female; average age, 78.8 years) with standardized documentation of VA, anecortave acetate 15 mg administered as a posterior juxtascleral depot injection was safe and well tolerated, based on near acuity, need for magnification, and fluorescein angiography.[73] The study concluded that in eyes with occult CNV without recent progression or with residual neovascular activity after PDT, anecortave acetate may be an alternative therapeutic option before considering intravitreal anti-VEGF agents due to its less invasive character and lower risk profile.

Several natural supplements or compounds derived from natural sources have been investigated in experimental models of CNV. Astaxanthin (AST), for example, is a carotenoid found in marine animals and vegetables that has been investigated for its effects on the development of experimental CNV in mice.[74] In this study, mice with laser photocoagulation-induced CNV who were treated with AST exhibited a significantly lower CNV volume as compared to vehicle-treated animals, suggesting that AST supplementation might be a viable therapeutic strategy for suppressing AMD-associated CNV.[74]

10.2 Radiotherapy in AMD

Radiotherapy represents a promising adjunct to anti-angiogenesis therapies for the control of CNV in AMD. However, even though modern delivery systems permit relatively low dosages, there are risks of radiotherapy to ocular tissue, and its role remains questionable in light of advances in pharmacotherapy.[75]

11. Conclusions

Treatment of AMD prior to 2000 was limited to focal laser photocoagulation, a destructive procedure that produced a permanent scar in an effort to limit the spread of CNV. This procedure turned out to be viable only for treating extra-foveal CNV, and even then, it was not entirely effective. PDT with verteporfin emerged in 2000 as the first treatment proven to reduce the risk of vision loss in sub-foveal CNV. However, its efficacy was limited to classic or small CNV, and even though it is a relatively nondestructive form of therapy, it failed to improve vision in patients with AMD in clinical trials.

AMD typically manifests as the loss of central vision; as such, it represents a major threat to quality of life. In addition, in a recent review of available data on the economic impact of macular degeneration in the developed world, which included reports of direct and indirect medical costs as well as estimates of non-healthcare costs, there were substantial differences in caregiver support with increased AMD severity. Thus, the development and testing of therapeutic agents that prevent or delay the progression of AMD is urgently needed, from the standpoint of patient care and quality of life, as well as cost savings.[76]

VEGF plays an important role in promoting angiogenesis, vascular leakage, CNV infiltration, and fluid accumulation in neovascular AMD. Therefore, inhibition of VEGF holds the promise of more effectively preventing or delaying the progression of neovascular AMD. Pegaptanib was approved by the FDA in 2004 and ranibizumab in 2006 after extensive preclinical and clinical testing. Off-label usage of bevacizumab has also become fairly standard. VA gains associated with ranibizumab have proven to be particularly exciting, and ranibizumab has become the current gold standard for AMD therapy. However, as with many new therapies, there are unresolved issues with anti-VEGF-based therapies, including safety, cost, and dosing frequency.

Additional preclinical and clinical studies are needed to assess the effects of inhibition of VEGF at various levels in AMD and beyond. Clinical trials assessing combination therapies, in particular, pegaptanib with ranibizumab and bevacizumab, as well as verteporfin PDT in various combinations with these drugs, are needed. In addition, studies are needed to assess adverse events outside those proposed in current trials,

determine optimal dosing regimens and the benefits of retreatment after initial treatment, and to review cost effectiveness in more detail. Finally, the relationship between duration of vision loss and quality of life and/or functional impact of vision loss, and behavioral studies of those genetically at risk for AMD are as-yet relatively unexplored areas of research in the field of AMD.[46]

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Regeneron Reports First Quarter 2008 Financial and Operating Results

TARRYTOWN, N.Y., May 01, 2008 (BUSINESS WIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced financial and operating results for the first quarter 2008. The Company reported a net loss of $11.6 million, or $0.15 per share (basic and diluted), for the first quarter of 2008 compared with a net loss of $29.9 million, or $0.46 per share (basic and diluted), for the first quarter of 2007.

At March 31, 2008, cash, restricted cash, and marketable securities totaled $827.9 million compared with $846.3 million at December 31, 2007. The Company's $200.0 million of convertible notes, which bear interest at 5.5 percent per annum, mature in October 2008.

Current Business Highlights

ARCALYST™ (rilonacept) - Inflammatory Diseases

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

A Phase 2 safety and efficacy trial of ARCALYST is underway in the prevention of gout flares induced by the initiation of uric acid-lowering drug therapy used to control gout. The Company is also evaluating the potential use of ARCALYST in other indications in which interleukin-1 (IL-1) may play a role.

Aflibercept (VEGF Trap) - Oncology

In their collaboration to develop aflibercept for the treatment of cancer, Regeneron and sanofi-aventis currently are enrolling patients in four Phase 3 trials that combine aflibercept with standard chemotherapy regimens. One trial is evaluating aflibercept as a 2nd line treatment for metastatic colorectal cancer in combination with folinic acid, 5-FU, and irinotecan. A second trial is evaluating aflibercept as a 1st line treatment for metastatic pancreatic cancer in combination with gemcitabine. A third trial is evaluating aflibercept as a 1st line treatment for metastatic androgen independent prostate cancer in combination with docetaxel/prednisone. The fourth trial is evaluating aflibercept as a 2nd line treatment for metastatic non-small cell lung cancer in combination with docetaxel. All four trials are studying the current standard of chemotherapy care for the cancer being studied with and without aflibercept. In addition, more than 13 studies are being conducted in conjunction with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) evaluating aflibercept as a single agent or in combination with chemotherapy regimens in a variety of cancer indications.

VEGF Trap-Eye - Eye Diseases

VEGF Trap-Eye is a specially purified and formulated form of the VEGF Trap for use in intraocular applications. Regeneron and Bayer HealthCare initiated a Phase 3 global development program of VEGF Trap-Eye in the neovascular form of Age-related Macular Degeneration (wet AMD) in the third quarter of 2007. The first trial, known as VIEW 1 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), is comparing VEGF Trap-Eye and ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.), an anti-angiogenic agent approved for use in wet AMD. The trial is evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye, compared with ranibizumab dosed every four weeks according to its label. Bayer HealthCare is initiating a second Phase 3 trial of VEGF Trap-Eye in wet AMD in the European Union and other parts of the world outside the U.S.

In April 2008, Regeneron and Bayer HealthCare announced the 32-week endpoint results of a Phase 2 study evaluating VEGF Trap-Eye in wet AMD, which were presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, Florida. The analysis showed that VEGF Trap-Eye dosed on a PRN (as-needed) dosing schedule maintained the statistically significant gain in visual acuity achieved after an initial 12-week, fixed-dosing phase.

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

Patients receiving monthly doses of VEGF Trap-Eye, either 0.5 or 2.0 mg, for 12 weeks followed by PRN dosing thereafter achieved mean improvements in visual acuity of 8.0 (p less than0.01 versus baseline) and 10.1 letters (p less than 0.0001 versus baseline), respectively, and mean decreases in retinal thickness of 141 (p less than 0.0001 versus baseline) and 162 microns (p less than 0.0001 versus baseline) at week 32, respectively.

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

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

Monoclonal Antibodies

Regeneron and sanofi-aventis are collaborating on the discovery, development, and commercialization of fully human monoclonal antibodies generated by Regeneron using its VelocImmune® technology. The first therapeutic antibody to enter clinical development under the collaboration is REGN88, an antibody to the interleukin-6 receptor (IL-6R) that is being evaluated in rheumatoid arthritis. A second antibody candidate, an antibody to Delta-like ligand-4 (Dll4), is slated to start clinical development in mid-2008. The Company and sanofi-aventis plan to advance two to three new antibodies into clinical development each year.

Financial Results

Revenue

Regeneron's total revenue increased to $56.4 million in the first quarter of 2008 from $15.8 million in the same period of 2007. Contract research and development revenue in the first quarter of 2008 principally related to the Company's aflibercept and antibody collaborations with sanofi-aventis and the Company's VEGF Trap-Eye collaboration with Bayer HealthCare. In the first quarter of 2007, contract research and development revenue primarily related to the Company's aflibercept collaboration with sanofi-aventis. Technology licensing revenue related to the Company's license agreements with AstraZeneca and Astellas.

Regeneron recognized contract research and development revenue of $13.8 million in the first quarter of 2008 related to the Company's aflibercept collaboration with sanofi-aventis, compared with $11.8 million in the same period of 2007. Contract research and development revenue from the collaboration consisted of reimbursement of aflibercept development expenses incurred by the Company plus recognition of amounts related to $105.0 million of previously received and deferred non-refundable, up-front payments. Reimbursement of expenses increased to $11.7 million in the first quarter of 2008 from $9.6 million in the same period of 2007, principally due to higher costs related to the Company's manufacture of aflibercept clinical supplies and higher clinical development costs. With respect to the $105.0 million of up-front payments from sanofi-aventis, $2.1 million was recognized in the first quarter of 2008 compared to $2.2 million in the same period of 2007.

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

Regeneron recognized contract research and development revenue of $21.9 million in the first quarter of 2008 related to the Company's antibody collaboration with sanofi-aventis. Contract research and development revenue from the antibody collaboration consisted of $15.1 million for reimbursement of the Company's expenses under the collaboration's discovery agreement, $4.2 million for reimbursement of the Company's REGN88 development expenses, and $2.6 million related to an $85.0 million non-refundable, up-front payment, which was deferred upon receipt in December 2007.

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

In the first quarter of 2008, the Company recorded $9.0 million of contract research and development revenue from Bayer HealthCare, consisting of $3.3 million related to the $75.0 million up-front licensing payment and the $20.0 million milestone payment and $5.7 million related to the portion of the Company's first quarter 2008 VEGF Trap-Eye development expenses that is reimbursable from Bayer HealthCare.

Regeneron has entered into non-exclusive license agreements with AstraZeneca and Astellas that allow those companies to utilize VelocImmune® technology in their internal research programs to discover human monoclonal antibodies. Each company made a $20.0 million up-front, non-refundable payment in 2007 and will make up to five additional annual payments of $20.0 million, subject to the ability to terminate their agreements after making three additional payments. Upon receipt, these payments are deferred and are recognized as revenue ratably over approximately the ensuing year of each agreement. Regeneron will also receive a mid-single-digit royalty on sales of any antibodies discovered utilizing VelocImmune. In the first quarter of 2008 and 2007, the Company recognized $10.0 million and $2.1 million, respectively, of technology licensing revenue related to these agreements.

ARCALYST™ (rilonacept) Product Sales

In late March 2008, the Company shipped $0.8 million of ARCALYST to its distributors, which was fully deferred at March 31, 2008 and classified as deferred revenue in the Company's financial statements.

Expenses

Total operating expenses for the first quarter of 2008 were $72.3 million, 46 percent higher than the same period in 2007. Our average headcount increased to 714 in the first quarter of 2008 from 585 in the same period of 2007 primarily as a result of our expanding research and development activities directed toward preclinical and clinical development of product candidates, including ARCALYST™, aflibercept, VEGF Trap-Eye, and monoclonal antibodies (including REGN88 and the Dll4 antibody).

Operating expenses included non-cash compensation expense related to employee stock option and restricted stock awards of $8.3 million and $6.6 million in the first quarters of 2008 and 2007, respectively.

Research and development (R&D) expenses increased to $61.3 million in the first quarter of 2008 from $41.2 million in the comparable quarter of 2007. The Company incurred higher R&D costs primarily related to additional R&D headcount, clinical development costs for VEGF Trap-Eye and ARCALYST, and costs related to manufacturing supplies of aflibercept, VEGF Trap-Eye, and the Dll4 antibody.

Selling, general, and administrative expenses increased to $11.0 million in the first quarter of 2008 from $8.2 million in the comparable period of 2007. In the first quarter of 2008, the Company incurred costs associated with the launch of ARCALYST. In addition, the Company incurred higher compensation expense and recruitment costs associated with expanding the Company's headcount, and higher legal fees related to general corporate matters.

Other Income

Investment income increased to $7.3 million in the first quarter of 2008 from $6.7 million in the comparable quarter of 2007. The increase in investment income resulted primarily from higher balances of cash and marketable securities, due primarily to receipts from sanofi-aventis of $312.0 million for the purchase of 12 million shares of the Company's Common Stock in December 2007 and the $85.0 million up-front payment related to the antibody collaboration, partially offset by lower effective interest rates in 2008.

About Regeneron Pharmaceuticals

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

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

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

	March 31, 2008	December 31, 2007
ASSETS		
Cash, restricted cash, and marketable securities	$827,858	$846,279
Receivables	32,960	18,320
Property, plant, and equipment, net	58,419	58,304
Other assets	11,639	13,355
Total assets	$930,876	$936,258
LIABILITIES AND STOCKHOLDERS' EQUITY		
Accounts payable and accrued expenses	$30,314	$39,232
Deferred revenue	239,959	236,759
Notes payable	200,000	200,000
Stockholders' equity	460,603	460,267
Total liabilities and stockholders' equity	$930,876	$936,258

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

	For the three months ended March 31, 2008	2007
Revenues		
Contract research and development	$46,383	$13,645

Technology licensing	10,000	2,143
	56,383	15,788
Expenses		
Research and development	61,270	41,235
Selling, general, and administrative	11,024	8,202
	72,294	49,437
Loss from operations	(15,911)	(33,649)
Other income (expense)		
Investment income	7,304	6,743
Interest expense	(3,011)	(3,011)
	4,293	3,732
Net loss	$(11,618)	$(29,917)
Net loss per share amounts, basic and diluted	$(0.15)	$(0.46)
Weighted average shares outstanding, basic and diluted	78,493	65,563

SOURCE: Regeneron Pharmaceuticals, Inc.

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REGENERON
science to medicine®

September 28, 2008

VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting

Regression of total active lesion caused by wet AMD reported

SCOTTSDALE, Ariz., Sep 28, 2008 (BUSINESS WIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare AG announced that VEGF Trap-Eye achieved durable improvements in visual acuity and in biologic measures of neovascular disease, including retinal thickness and active choroidal neovascularization lesion size, for up to one year in a Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD). The results were reported today in two oral presentations at the 2008 annual meeting of the Retina Society in Scottsdale, Arizona. Slides, including data reported at the presentations, are available on the Regeneron website (www.regeneron.com on the Presentations Page, under the Investor Relations section).

In this double-masked Phase 2 trial, patients were initially treated with either fixed monthly or quarterly dosing for 12 weeks and then continued to receive treatment for another 40 weeks on a PRN (as needed) dosing schedule. Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline of 9.0 letters ($p<0.0001$ versus baseline) and 5.4 letters ($p<0.085$ versus baseline), respectively, at the end of one year. The proportion of patients with vision of 20/40 or better (part of the legal minimum requirement for an unrestricted driver's license in the U.S.) increased from 23 percent at baseline to 45 percent at week 52 in patients initially treated with 2.0 mg monthly and from 16 percent at baseline to 47 percent at week 52 in patients initially treated with 0.5 mg monthly. During the week 12 to week 52 PRN dosing period, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.

Patients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 mg for 12 weeks followed by PRN dosing also achieved mean decreases in retinal thickness versus baseline of 143 microns ($p<0.0001$ versus baseline) and 125 microns ($p<0.0001$ versus baseline) at week 52, respectively.

While PRN dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity and retinal thickness versus baseline at week 52, the results generally were not as robust as those obtained with initial fixed monthly dosing.

"Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD, and improvement in visual acuity is now feasible in most patients. The biggest challenge we have is that with our current drugs, the majority of patients need frequent injections into their eye to maintain their visual acuity gains," stated David M. Brown, M.D., a study investigator and a retinal specialist at The Methodist Hospital in Houston. "These study results reinforce our interest in further exploring whether continued administration of VEGF Trap-Eye on an as-needed basis after an initial period of fixed dosing can maintain a durability of effect over time in controlled Phase 3 clinical studies."

In this Phase 2 study VEGF Trap-Eye was also associated with a reduction in the size of the total active choroidal neovascular membrane (CNV), the active lesion that is the underlying cause of vision loss in patients with wet AMD. Patients initially receiving either a 2.0 mg or 0.5 mg monthly fixed dose of VEGF Trap-Eye for 12 weeks followed by PRN dosing experienced statistically significant 3.41 mm(2) and 1.42 mm(2) reductions in mean CNV size at 48 weeks (the final one-year analysis from the independent reading center) versus baseline, respectively. Patients in the 2.0 mg monthly cohort also achieved a statistically significant 1.75 mm(2) reduction in total lesion size. A reduction in total lesion size was not seen in the cohort initially dosed with 0.5 mg monthly.

"Progression of the active CNV lesion and resulting vision impairment are inevitable consequences of untreated wet AMD. The reduction in total active CNV lesion size achieved with VEGF Trap-Eye treatment in this Phase 2 clinical study could potentially translate into clinically meaningful outcomes in the larger, controlled Phase 3 studies that are underway," stated Jason Slakter, M.D., head of the independent reading center for the study and a Clinical Professor of Ophthalmology, New York University School of Medicine, New York.

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

"These study results confirm the rationale for our Phase 3 clinical program for VEGF Trap-Eye in wet AMD," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "These trials are designed to optimize improvement in visual acuity with fixed-dosing regimens of either every 4 weeks or every 8 weeks for one year and then study how these vision improvements can be maintained with as-needed dosing in the second year."

About the Phase 2 Study in Wet AMD

In the double-masked, prospective, randomized, multi-center Phase 2 trial, 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity. The primary endpoint results from the fixed dosing period were presented at the 2007 Retina Society conference in September 2007. Week 32 results were presented at the 2008 Association for Research in Vision and Ophthalmology annual meeting in April 2008.

About the Phase 3 Program in Wet AMD

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

About VEGF Trap-Eye

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

About Wet AMD

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

About Regeneron Pharmaceuticals, Inc.

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Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital,

the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2007 and Form 10-Q for the quarter ended June 30, 2008. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

SOURCE: Regeneron Pharmaceuticals, Inc.

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OBS 1

VEGF Trap-Eye in Wet AMD
CLEAR-IT 2: Summary of One-Year Key Results

Presented at 2008 Retina Society Meeting
Scottsdale, Arizona
September 28, 2008

A Phase 2, Randomized, Controlled
Dose- and Interval-Ranging Study
of Intravitreal VEGF Trap-Eye
in Patients With Neovascular,
Age-Related Macular Degeneration

CLEAR-IT 2: Rationale

- Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD
  - Improvement in visual acuity is now an achievable goal of treatment
- A potential limitation of anti-VEGF therapy is the unpredictable durability of vision gain initially achieved with monthly dosing when the treatment interval is prolonged
- VEGF Trap-Eye is a novel anti-VEGF therapy with high binding affinity for VEGF-A and placental growth factor (PlGF)
- CLEAR-IT 2 was designed to assess:
  - Response at 12 weeks to a range of doses administered monthly and quarterly
  - Durability of response with PRN (as-needed) dosing out to 1 year

CLEAR-IT 2: Study Design

Randomized, multicenter, double-masked trial
N=154

0.5 mg q4 wks n=32

2 mg q4 wks n=32

0.5 mg q12 wks n=32

2 mg q12 wks n=32

4 mg q12 wks n=31

Primary endpoint:
Change in Central Retinal Lesion Thickness (CRLT)

Fixed dosing to week 12 (primary endpoint)

Secondary endpoint:
Best-Corrected ETDRS Visual Acuity (BCVA)

PRN dosing to 1 year

Patients were re-dosed at week 12; PRN dosing started at week 16

Study Schedule
(fixed-dosing phase)
Weeks
0
4
8
12
0.5 mg q4 wks
0.5 mg q12 wks
2 mg q4 wks
2 mg q12 wks
4 mg q12 wks
Primary and Secondary
Endpoints
0.5 mg q4 wks VEGF Trap
0.5 mg q12 wks VEGF Trap
2 mg q12 wks VEGF Trap
2 mg q4 wks VEGF Trap
4 mg VEGF Trap

Study Schedule
(fixed-dosing phase)

Study Schedule
Weeks
0
4
8
12
16
0.5 mg q4 wks
0.5 mg q12 wks
2 mg q4 wks
2 mg q12 wks
4 mg q12 wks
prn
…1 year
Primary and Secondary Endpoints
0.5 mg q4 wks VEGF Trap
0.5 mg q12 wks VEGF Trap
2 mg q4 wks VEGF Trap
2 mg q12 wks VEGF Trap
4 mg VEGF Trap
6

Baseline Characteristics

(n=157*)

	Mean	Range
Age (years)	78.2	53-94
Gender (% M:% F)	38:62	
Disease Duration (months)	3.9	0-67
Lesion Size (mean±SD) in disc areas	3.1±2.12	
Lesion Type: number (%)		
Classic	30 (19.1)	
Predominantly Classic	30 (19.1)	
Minimally Classic	37 (23.6)	
Occult Lesions	60 (38.2)	
Disease Status		
Central Retinal/Lesion Thickness	456 µm	186-1316 µm
Foveal Thickness	327 µm	116-1081 µm
ETDRS BCVA (letters)	56	27-83

*N=159 randomized; n=157 treated

Patient Disposition

No. of Patients	0.5 q4	0.5 q12	2 q4	2 q12	4 q12	All Patients
Screened						301
Randomized	32	32	32	32	31	159
Treated	32	32	31	31	31	157
Completed Wk 52	26	26	29	27	26	134 (84.3%)
Withdrawn by Wk 52	6	6	2	4	5	23 (14.5%)
Reason for Withdrawal						
Non-compliance					1	1 (0.6%)
Subject request	3			2	1	6 (3.8%)
Adverse event				1		1 (0.6%)
Investigator decision	1	1				2 (1.3%)
Sponsor decision	1	1			1	3 (1.9%)
Lost to follow-up		2	1			3 (1.9%)
Death			1		1	2 (1.3%)
Other	1	2		1	1	5 (3.1%)

Primary Endpoint Results: Reported at 2007 Retina Society

At 12 weeks VEGF Trap-Eye:

- Significantly improved mean visual acuity
- Significantly reduced central retinal thickness
- Groups dosed at Baseline and at Week 12 showed improved visual acuity and retinal thickness
  - Effect was not as robust as with monthly dosing
- Maintained effect on visual acuity with a single dose to 8 weeks
- Was generally well tolerated with no drug-related serious adverse events

Number of Doses Administered

10

Re-dosing Criteria
(starting at week 16)

- Increase in central retinal thickness of ≥100μm as measured by OCT, or;
- A loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or;
- Persistent fluid as indicated by OCT, or;
- New onset classic neovascularization, or;
- New or persistent leak on FA, or;
- New macular hemorrhage

Re-Treatment Outcome

Number of injections over PRN phase*

VEGF Trap-Eye	Mean	Median	Range
0.5 mg q4	2.52	2	0 – 9
2 mg q4	1.55	1	0 – 4
0.5 mg q12	1.84	2	0 – 4
2 mg q12	2.48	3	0 – 5
4 mg q12	1.7	1	0 – 7
All	**2.01**	2	0 – 9

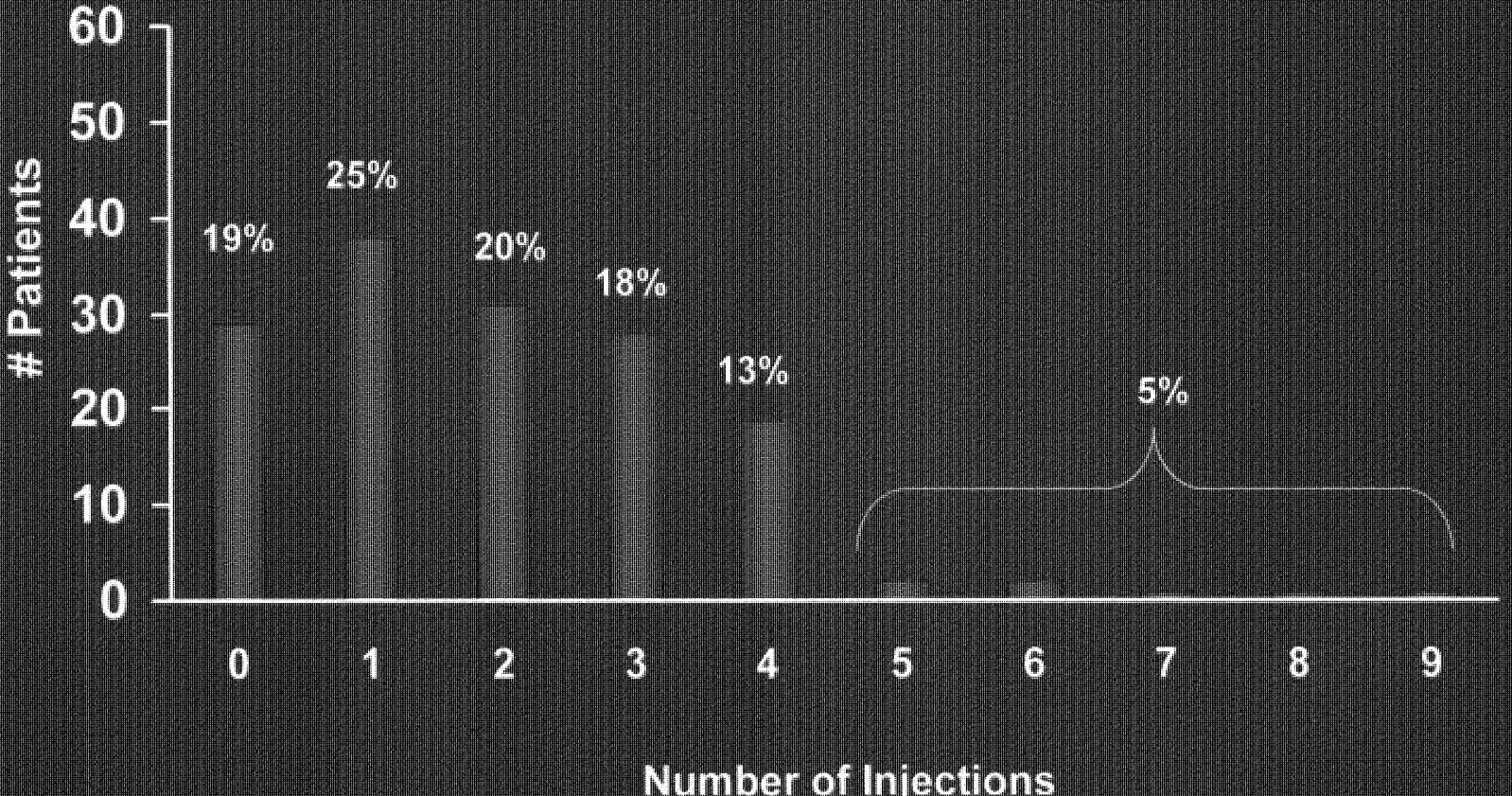
All patients, n=152

* After the week 12 injection through week 52

Re-Treatment Outcome

VEGF Trap-Eye	Mean number of injections over PRN phase (week 12 – 52)	Mean number of days to first injection over PRN phase (week 12 – 52)	Median number of days to first injection over PRN phase (week 12 – 52)
0.5 mg q4			85
2 mg q4			150
0.5 mg q12			86
2 mg q12			86
4 mg q12			111
All			110

Distribution of Injections over PRN Phase (All groups combined)



Percent of patients receiving an injection analyzed by number of injections, n=152

Kaplan-Meier Curve
Time to Re-injection (by treatment group)
Time to 1st re-injection
0.5q12
0.5q4
2.0q12
2.0q4
4.0q12
Censored
Median # of days to 1st re-injection in 2.0q4 group = 150
Percent Patients
100
80
60
40
20
0
0
100
200
300
400
Days
15

Mean Change in Visual Acuity
Change in Visual Acuity (letters)
Fixed-dosing
PRN-dosing Phase
9.0†
6.4†
4.2‡
2.6†
2q4
0.5q4
2q12
0.5q12
4q12
12
10
8
6
4
2
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
0.5q4
2q4
0.5q12
2q12
4q12
†P < 0.0001
‡P = 0.0154
‡‡P = 0.0412
†P = 0.085
††P = 0.344
LOCF analysis; paired t-test; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31
17

Mean Change in Central Retinal/Lesion Thickness
Fixed-dosing
PRN-dosing Phase
Week
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Change in CR/LT (microns)
0 -50 -100 -150 -200 -250
-109* 0.5q12
-161† 4q12
*P < 0.0001
†P = 0.0002
0.5q4
2q4
0.5q12
2q12
4q12
Posterior Pole Scans; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31
18

Visual Acuity at Week 52
Patients (%)
100%
80%
60%
40%
20%
0%
88%
100%
88%
90%
97%
78%
81%
74%
71%
58%
29%
19%
29%
22%
10%
<15 letters lost
≥ 0 letter gain
≥ 15 letter gain
0.5q4
2q4
0.5q12
2q12
4q12
LOCF analysis; 0.5q4 and 0.5q12 n=32; 2q4, 2q12, and 4q12; n=31
19

Proportion of Patients
With ≥ 20/40 Vision
Patients (%) With
≥20/40 Vision
50%
40%
30%
20%
10%
0%
47%
16%
45%
23%
45%
22%
34%
10%
39%
16%
BL Wk52
BL Wk52
BL Wk52
BL Wk52
0.5q4
2q4
0.5q12
2q12
2q12
4q12
Dose Groups
LOCF analysis: 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31 BL=baseline
20

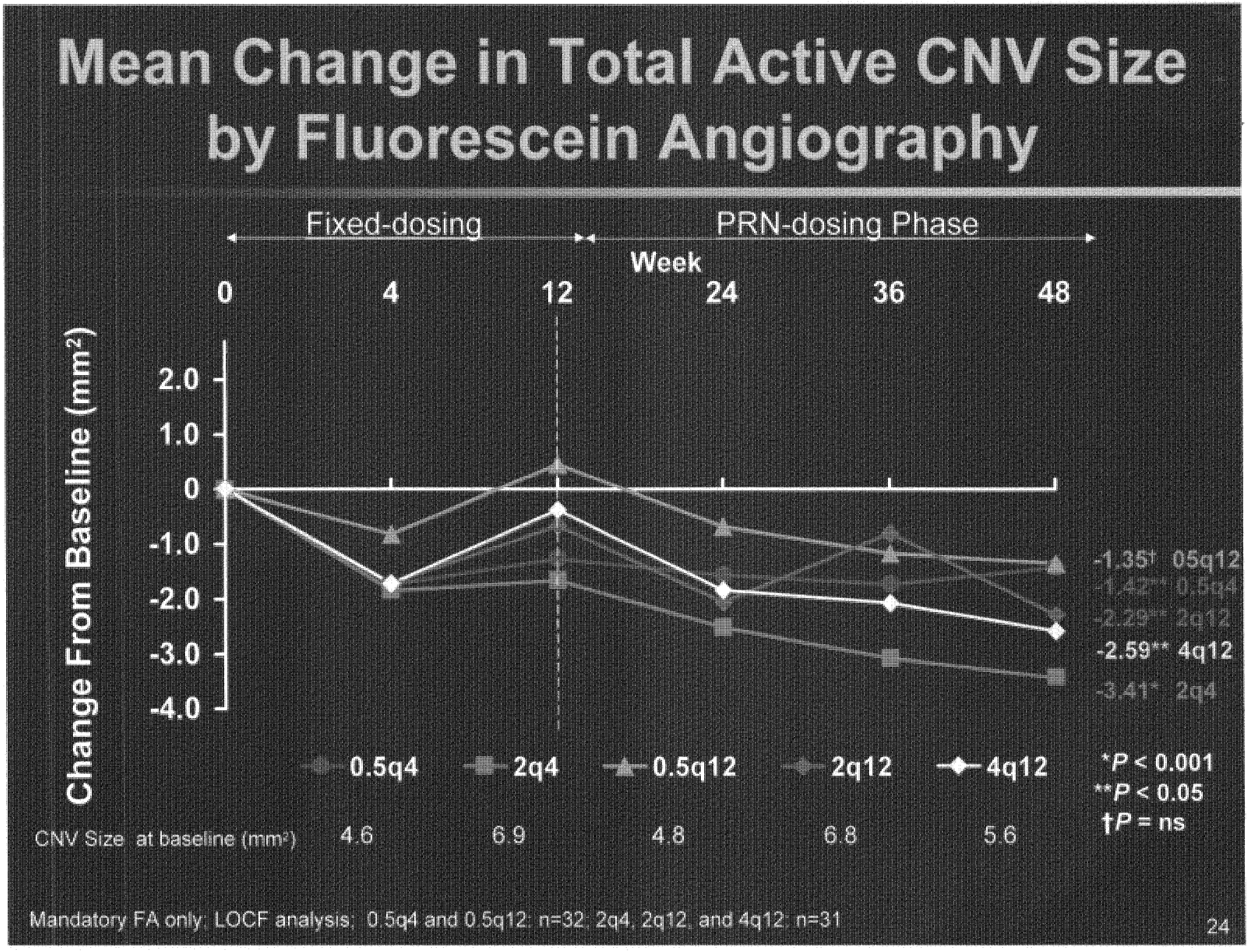
Fluorescein Angiography 1-Year Outcomes

21

DARC Reading Center: Definitions

- Total Lesion Size
  - Measurement of entire lesion including the classic and occult neo-vascular component as well as contiguous areas of blood and/or blocked fluorescence and/or serous pigment epithelial detachment (PED)
- Total Active CNV Size
  - Area of visible CNV (classic and/or occult) which demonstrates angiographic evidence of late leakage or pooling of dye
- Classic CNV
  - Area of bright, well-demarcated hyper-fluorescence in early phase, with progressive dye leakage into overlying sub-sensory retinal space in late phase of angiogram (not a measurement of area of leakage, but rather extent of the classic neo-vascular complex)
- Occult CNV
  - Angiogram shows staining or leakage from fibro-vascular PED or hyper-fluorescent leakage at level of RPE that represents late leakage of undetermined source (leakage in late phase without classic CNV or fibro-vascular PED to account for leakage)

Mean Change in Total Lesion Size by Fluorescein Angiography
Change From Baseline (mm²)
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
Fixed-dosing
PRN-dosing Phase
0.85‡ 0.5q12
0.01† 0.5q4
-0.04‡ 2q12
-1.00‡ 4q12
-1.75‡ 2q4
0
4
12
24
36
48
Week
0.5q4
2q4
0.5q12
2q12
4q12
Lesion Size at Baseline (mm²)
4.9
7.4
5.5
7.6
6.5
*P = 0.04
†P = NS
Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31
23



Mean Change in Classic CNV Size by Fluorescein Angiography
Fixed-dosing
PRN-dosing Phase
Week
0
4
12
24
36
48
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
Change From Baseline (mm²)
All P values ≤ 0.013
0.5q4
2q4
0.5q12
2q12
4q12
Classic CNV Size at Baseline (mm²)
1.2
1.2
1.8
1.8
1.3
Mandatory FA only; LOCF analysis: 0.5q4 and 0.5q12: n=32; 2q4, 2q12 and 4q12: n=31
25

Safety: Serious Adverse Events

Ocular Serious Adverse Events in the study eye:

- 1 case of culture-negative endophthalmitis / uveitis
  (deemed not related to study drug)

Systemic Serious Adverse Events:

- None deemed to be drug-related
- 2 deaths
  - Pulmonary hypertension (pre-existing condition)
  - Pancreatic carcinoma
- Arterial Thromboembolic Events (ATE's): 1 case of hemorrhagic stroke
  - Subject had a history of prior stroke

Adverse Events

(Study eye, all groups combined ≥ 5%)

Adverse Event	Number (N=157)	Percent (%)
Conjunctival Hemorrhage	60	38.2
Increased IOP (transient post-injection)	29	18.5
Refraction Disorder	25	15.9
Retinal Hemorrhage	23	14.6
Visual Acuity Reduced (patient reported)	21	13.4
Vitreous Detachment	18	11.5
Eye Pain	15	9.6
Vitreous Floaters	14	8.9
Detachment of Retinal Pigment Epithelium	12	7.6
Retinal Edema	10	6.4
Visual Disturbance	9	5.7
Blepharitis	8	5.1
Cataract nuclear	8	5.1
Subretinal Fibrosis	8	5.1

IOP=intraocular pressure

Conclusions

- Patients received, on average, only two additional injections over 40-week PRN-dosing phase (after a 12-week fixed dosing period)
  - 19% received no additional injections after Week 12
  - 110 days median time to first re-injection
- VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over 1 year
  - Up to +9.0 mean letters gained at week 52
  - Up to -161 microns reduction in central retinal lesion thickness at week 52 as measured by OCT
- Generally well tolerated with no drug-related serious adverse events
  - Most common AE's typical of intravitreal injection

VIEW 1 & VIEW 2 Phase 3 Studies
(Dosing Schedule-Years 1 and 2)

Week 0 4 8 12 16 20 24 28 32 36-51* 52 52 – 96
Capped PRN †

0.5 mg q4 wks
2.0 mg q4 wks
2.0 mg q8 wks†
Ranibizumab 0.5 mg q4 wks

Primary and Secondary Endpoints Measured

*Continued dosing at their respective intervals
†After a loading dose period of 3-months
‡ Capped PRN: minimum injection frequency is q12 weeks

0.5 mg VEGF Trap
2 mg q4 wks VEGF Trap
2 mg q8 wks VEGF Trap
0.5 mg Ranibizumab

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Contact Customer Services at www.epo.org/contact

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Date
13.09.2016

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325

Applicant/Proprietor
Regeneron Pharmaceuticals, Inc.

Communication pursuant to Rule 114(2) EPC

Please find enclosed observations by a third party concerning the patentability of the invention of the above-mentioned patent application. That person is not a party to the proceedings before the EPO (Art. 115 EPC).

Under Rule 114(2) EPC you may comment on the observations.

For the Examining Division

European Patent Office
Bob-van-Benthem-Platz 1
80469 Munich

Anonymous third party observation regarding EP 12700590.8

This is a Third Party Observation pursuant to Article 115 EPC in respect of pending European Patent Application EP12700590.8/2663325 (hereinafter "application") filed on 11 January 2012 in the name of Regeneron Pharmaceuticals, Inc.

The subject matter of the set of claims as filed on 17 December 2014 and currently pending in the application is not patentable under the terms of Articles 52-57 EPC.
Furthermore, the claimed subject matter is not disclosed in the application in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

I. Pertinent Documents

In the following it is referred to document *D13* cited as such in the Examination Procedure, as well as documents *OBS1-OBS8*, which are considered highly relevant with regard to patentability

of the claimed subject matter, all of which represent prior art according to Article 54(2) EPC.

D13: XP002674126

OBS1: Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008

OBS2: Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008

OBS3: Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007

OBS4: WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119

OBS5: Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8

OBS6: Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009

OBS7: Mousa and Mousa, Biodrugs 2010; 24(3); 183-194

OBS8: Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

II. Claims pending in the application

Claim 1 is the sole independent claim currently pending in the application and relates to:

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 **[feature a]**
followed by
- two or more secondary doses of the VEGF antagonist **[feature b]**,
followed by
- one or more tertiary doses of the VEGF antagonist **[feature c]**;
wherein
- each secondary dose is administered 4 weeks after the immediately preceding dose **[feature b1]**;
wherein
- each tertiary dose is administered 8 weeks after the immediately preceding dose **[feature c1]**;
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 **[feature d]**;
and wherein
- the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1 **[feature e]**.

The remaining dependent claims will be referred to in the respective passages below, if applicable.

III. Novelty of the Subject Matter of Claims 1-12

The subject matter of independent claim 1 is not novel over documents *D13*, *OBS1* and *OBS2*.

Independent claim 1 is a second medical use claim, which use is in a treatment of particular angiogenic eye disorders **[feature d]**, characterized by a particular dosage regimen **[features a - c]** of a specific VEGF antagonist **[feature e]**.

The exact same dosage regimen was used in Regeneron's phase 3 trial "VIEW 2" and in this context was available to the public long before the earliest priority date of 13 January 2011.
Evidence for the public availability of the critical details of the VIEW 2 study is provided by prior art documents *D13*, *OBS1* and *OBS2*:

D13, also cited by the Examining Division in the Examination Procedure, describes at page 2 third paragraph, that Regeneron's phase 3 trial aims *inter alia* at "evaluating VEGF TRAP-Eye dosed [...] 2 mg every 8 weeks (following 3 monthly doses)". Such a dosage regimen is covered by claim 1 as it comes down to administering the VEGF antagonist at week 0 **[feature a]**, week 4 and 8 **[feature b1]** and week 16 **[feature c1]**.

Similarly, this dosage regimen was also presented at the 2008 Retina Society Meeting as can be seen from the table at page 29 of *OBS1*, which shows a dosage regimen (row labeled "2.0 mg q8 wks") falling within the definition of that recited in claim 1.

A dosage regimen as claimed is furthermore foreseen in the "Descriptive Information" of this VIEW 2 Clinical Trial, available online in its version of 17 March 2008 (see the third Intervention "Arm 3" at page 2 of *OBS2*).

While in the above cited documents (*D13*, *OBS1*, *OBS2*) the tested compound is denominated "VEGF TRAP-Eye", this designation was known at the priority date of the application for a person skilled in the art as a synonym for "aflibercept" which is encoded by SEQ ID NO:1. Importantly, structural information concerning VEGF TRAP-Eye/aflibercept was at the disposal of the person skilled in the art since 2006, as is apparent from documents *OBS3-OBS8* as follows:

OBS3 is a quality report published on 7 November 2007 by the applicant Regeneron. Such a quality report as required by the US Security and Exchange Commision is immediately available on the internet.

In particular at page 15 and 17 of *OBS3* "VEGF TRAP" is identified as "aflibercept" and at page 19 it is stated that "VEGF TRAP-Eye is a form of the VEGF TRAP [...] suitable for direct injection into the eye". Comparable information is also contained in *OBS8.* From here it is clearly apparent that VEGF TRAP-Eye is aflibercept.
The fact that these two terms are synonym is also acknowledged by the Examining Division (see e.g. item 5 of the Communication dated 21 August 2014).

Knowing that the compound tested in the VIEW 2 trial publicized by *D13* and *OBS1-OBS2* is aflibercept, the person skilled in the art also was in a position to obtain the relevant structural information as such information was available, e.g. from:

OBS4, which is a 2006 report of the WHO that discloses on pages 118 and 119 the chemical structure, i.e. the amino acid sequence of aflibercept, which
- comprises the three elements aa 27-129, aa 130-231 and aa 232-457 of SEQ ID NO:2 of the present application that are characteristic for VEGFR1R2-FcΔC1(a) (as specified in par. [0023] of the specification of the present application), and
- is encoded by SEQ ID NO:1 of the present application **[feature e]**.

Of note, this peptide sequence of aflibercept is identical with the sequence of the particular VEGF antagonist of claim 7 having an amino acid sequence defined by residues 27 to 457 of SEQ ID NO:2 of the application.

Additionally, also documents *OBS5-OBS7* represent the knowledge of a person skilled in the art with respect to the structure of VEGF TRAP-Eye/aflibercept, namely:

OBS5 states at page 3, left column, third paragraph that "VEGF TRAP-Eye and aflibercept" (the oncology product) have the same molecular structure" and this reference also discusses the VIEW 2 study, namely its "bimonthly" **[feature c1]** dosage regimen (see page 4, right column, second paragraph and page 5, right column, first paragraph).

Similarly, *OBS6* states at page 1559, right column, that "aflibercept [is] also known as a VEGF Trap-Eye" and further outlines the structure of this fusion protein. Interestingly, this review focuses on treatment of diabetic retinopathy hence underlining the comparable requirements for the treatment of the different angiogenic diseases **[feature d]** recited in the pending claims.

Finally, *OBS7* repeats the identity of aflibercept and VEGF Trap-Eye and also points to the VIEW 2 study (see page 187).

From the foregoing, it is apparent that there can be no doubt that the person skilled in the art at the earliest priority date was aware that the compound to be tested in the VIEW 2 trial, which trial used the claimed dosage regimen, is aflibercept and its detailed structure being known since 2006.

In light of the above, the subject matter of claims 1 and 7 can by no means be regarded as novel.

As the subject matter of claims 2-6 consists in a mere subdivision of the different diseases listed in claim 1 **[feature d]**, the ascertained lack of novelty likewise applies to the subject matter of these claims.

Claims 8-10 specify administration routes, namely claim 8 pertains to "topical" or "intraocular" administration (the latter being also the subject matter of claim 9), and claim 10 further specifies "intraocular" as being "intravitreal".
While "intraocular" injection of VEGF Trap-Eye is e.g. disclosed at pages 18 and 19 of *OBS3*, the more specific "intravitreal" administration corresponds to the administration route used in the VIEW 2 trial as it is e.g. apparent from the Official title of the study (see *OBS2*): "A Randomized, Double Masked, Active Controlled, Phase 3 study of the Efficacy, Safety and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)" and the Conclusion section on page 28 of *OBS1*.
The features of claims 8-10 are thus not novel as well.

Claim 11 further specifies with respect to claim 1 that "all doses comprise from about 0.5 mg to about 2 mg" of the VEGF antagonist and claim 12 is restricted to the respective end points with claim 12(a) reciting "0.5 mg" and claim 12(b) reciting "2 mg".
These particular doses are anticipated by the VIEW 2 clinical trial (see *D13*; *OBS1* page 29; and *OBS2*) and thus lacks novelty

Claim 12(a) and (b) further specify that "all doses of the VEGF antagonist comprise 0.5 mg/2 mg of the VEGF antagonist", respectively. The use of constant amounts of aflibercept/VEGF Trap-Eye in the VIEW 2 trial is known from page 29 of *OBS1*.
The features of claim 11 and 12 are thus not novel.

The subject matter of claims 1-12 currently pending in the application thus contravenes Article 54 EPC.

IV. Inventive Step and Sufficiency of Disclosure of the Subject Matter of Claims 8-11 and 12

The alternative potential administration route recited in claim 8 that is not known from *OBS*1-3, i.e. "topical administration" which according to paragraph [0028] of the application is an administration "via eye drops or other liquids, gels, ointment or fluid", though certainly desirable as it would overcome the disadvantages associated with intravitreal injections such as being invasive and thus requiring a skilled specialist. However as this administration route is not supported by any data in the application it is hence to be regarded as an obvious alternative to the intraocular administration that is readily available to a person skilled in the art, i.e. lacks an inventive step.
Even more, the absence of experimental evidence gives rise to the conclusion that topical administration does not provide a solution to the technical problem of treating angiogenic eye disorder with a VEGF antagonist.

Similarly, regarding lower doses of 0.5 mg (claim 12(a)) or between 0.5 and 2 mg (claim 11) it has to be noted that these doses do not appear to contribute to an inventive step of the claimed second medical use.
This because, first, the exact value of 0.5 mg corresponds to the amount also used in the "VIEW 2" and previous Regeneron trials in connection with a monthly dosage regimen and further it is the effective concentration at which Ranibizumab is used in these studies for comparison (see *D13*, *OBS1* and *OBS2*). Therefore the choice of this minimal dose seems to be an obvious one for the person skilled in the art.
Second, the application does not even provide any data of the combination of "0.5 mg" and "bimonthly dosing" **[feature c1]**, so that it is questionable whether this dosage regimen solves the technical problem of providing an improved treatment of angiogenic eye disorders with a VEGF antagonist, at all.

The remarks above with regard to the lack of an inventive step for the subject matter of claims 11 and 12(a), namely that there are no supporting data on file demonstrating the effect of these administration regimens also give rise to a lack of sufficiency of disclosure.

The set of claims currently pending in the application thus also contravenes Articles 56 and/or 83 EPC.

In conclusion, the set of claims pending in European Patent Application EP12700590.8/2663325 does not fulfill the requirements of the EPC and should thus not be allowed by the Examining Division.

Encl: *OBS1-OBS8*

ANNEX 3

Article Date: 3/1/2010

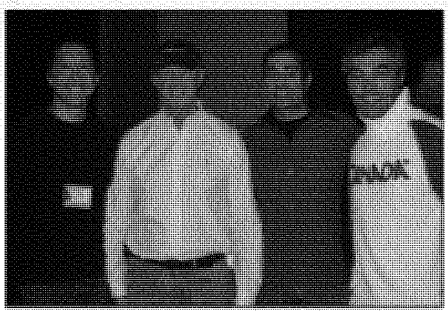
SUBSPECIALTY NEWS

Fellows Forum Marks 10th Year

Dr. Steve Charles is Guest Lecturer.

■ The tenth annual Retina Fellows' Forum took place on Jan. 29 and 30 at the Westin River North in frigid Chicago. Eighty North American fellows participated in an educational and social program that has become a much-anticipated fixture of the final year of vitreoretinal training.

As in past years, the fellows spent considerable time in the lecture hall with a panel of volunteer faculty, led by Course Director David Chow, MD, and co-directors Carl Awh, MD, and Tarek Hassan, MD. Ophthalmologists Dean Eliott, Phil Ferrone, Jeff Heier, Nancy Holekamp and Peter Kaiser completed the faculty.



From left, Drs. Carl Awh, Steve Charles (Distinguished Guest Lecturer), Tarek Hassan and David Chow.

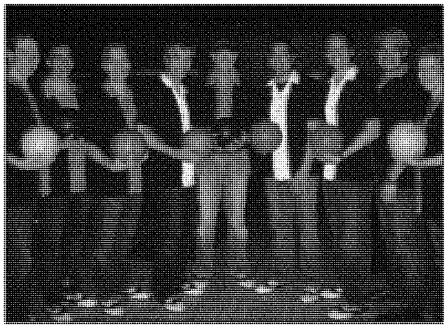
The meeting began on Friday evening with an AMD Symposium and sessions on Diagnostic Instrumentation and Pediatric Retina. New to the meeting were the inaugural "Faculty Debates," in which the faculty debated the following topics: Avastin vs. Lucentis; Pneumatic Retinopexy vs. Scleral Buckle vs. Vitrectomy, and Fluorescein Angiography vs. OCT. Topics were assigned to the faculty, who relied upon clinical data, personal experience, and (most effectively) humor to defend their positions.

A Friday evening reception and dinner provided the first opportunity for the "graduating class" of 2010 fellows to socialize with their peers, the faculty, and representatives from industry.

Saturday offered a full day of panel-driven discussions on Diabetic Retinopathy, Retinal Vascular Occlusion, Medical and Surgical "Pearls," "News You Can Use," and advice on career and lifestyle management. As always, a highlight of the meeting was the Distinguished Guest Lecture, this year delivered by Steve Charles, MD. Dr. Charles captivated and inspired the audience with his talk on "Technology, Technique, and the Pursuit of Happiness."

For the 10th consecutive year, Bausch & Lomb provided essential support as the major sponsor of the Retina Fellows' Forum. Genentech provided a generous educational grant to support the opening AMD symposium. Thirteen additional companies representing a cross-section of devices and services important to vitreoretinal practice provided financial support and presented updates to the group about their businesses.

The prestigious and competitive Bausch & Lomb Retina Fellows' Forum Research award went to Arghavan Almony, MD, of the Barnes Retina Institute for her paper, "Small-Gauge Vitrectomy Does Not Protect Against Nuclear Sclerotic Cataract." Dr. Almony will present her paper at the 2010 Annual Meeting of the American Society of Retina Specialists as a specially recognized lecture.



The Fellows Forum faculty, from left, Drs. Phil Ferrone, Jeff Heier, Dean Eliott, David Chow, Steve Charles, Tarek Hassan, Carl Awh, Peter Kaiser, and Nancy Holekamp.

The meeting concluded with dinner, an informal awards ceremony, and the 5th Annual Retinal Fellows' Forum Bowling Tournament. Fellows and corporate representatives were divided into teams captained by the faculty. Phil Ferrone's team emerged victorious, aided in no small measure by his score of 220, the highest of the evening.

The 11th Annual Retina Fellows Forum will be held in Chicago on Friday, Jan. 28 through Saturday, Jan. 29, 2011.

In addition to Bausch & Lomb and Genentech, corporate support for the event was provided by Alcon, Alimera Sciences, Allergan, Carl Zeiss Meditec, Dutch Ophthalmic, Insight Instruments, Iridex, MedOne Surgical, Neovista, QLT, Quantel Medical, Synergetics and Volk Optical.

VEGF Trap Has Positive DME Data

Study Compared Drug to Laser.

■ Regeneron Pharmaceuticals and Bayer HealthCare AG reported that VEGF Trap-Eye showed positive interim results versus laser in a phase 2 study in patients with diabetic macular edema.

The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME — macular laser therapy — was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the one-year study.

"The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high levels of vascular endothelial growth factor are present," said Diana Do, MD, the principal investigator for the study and assistant professor of Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine in Baltimore.

Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared to patients receiving macular laser therapy (2.5 letters gained) at week 24. VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.

In this double-masked, prospective, randomized, multicenter phase 2 trial, entitled DA VINCI, 219 patients with clinically significant DME with central macular involvement were randomized to five groups. The control group received macular laser therapy at week one, and patients were eligible for repeat laser treatments, but no more frequently than at 16-week intervals. Two groups received monthly doses of 0.5 or 2.0 mg of VEGF Trap-Eye throughout the six-month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every eight-week dosing or as-needed dosing with specific repeat dosing criteria. Patients are continuing on the same dosing regimens for an additional 24 weeks.

Avastin Seen as Equal to Lucentis

But Genentech Takes Issue With Study.

BY JERRY HELZNER, SENIOR EDITOR

■ Researchers at Kaiser Permanante Southern California who treated 324 wet AMD patients with Avastin (bevacizumab) and 128 patients with the same disease with Lucentis (ranibizumab) found little difference between the two Genentech drugs after 12 months, both in terms of stabilizing visual acuity and in reported side effects.

Genentech was quick to point out factors that could have biased the data.

The researchers, who reported their results in the February issue of *Ophthalmology*, acknowledged the observational and nonrandomized nature of the study. However, lead author Donald Fong, MD, said that the study "should reassure patients and ophthalmologists that bevacizumab appears to be just as effective as ranibizumab."

Though the Permananente study was uncontrolled and the bevacizumab patients had an average age of 78, significantly younger than the ranibizumab patients, the researchers found that approximately one-quarter of all patients achieved close to 20/40 vision at 12 months, with little difference in adverse events.

The larger and more rigorous CATT study, which will compare Avastin and Lucentis on a head-to-head basis, is currently underway. Initial results are expected sometime in 2011.

Genentech took issue with some aspects of the Kaiser Permanente study. In a prepared statement, the company said:

"We are aware of the retrospective analysis published in the journal *Ophthalmology* titled 'Intravitreal Bevacizumab and Ranibizumab for Age-Related Macular Degeneration.' Genentech continues to believe Lucentis is the most appropriate medicine for people with wet age-related macular degeneration because it was specifically designed, formally studied, manufactured for intraocular delivery and is approved by FDA. At the same time, Genentech does not interfere with doctors' prescribing choices and believes that they should be able to prescribe the treatment they believe is most appropriate for their patients."

Genentech further asserted that "this was an uncontrolled and unmasked retrospective case analysis, with too few patients and too short a duration to adequately assess differences between the two treatment groups."

Genentech quoted Dr. Fong as stating in the article that "the sample size of the current study does not have sufficient power to determine whether there are any differences in safety." The author also notes in the conclusion of the paper, "Because the study is a nonrandomized comparison, selection bias could mask a true treatment difference."

According to Genentech, "The results beg the question as to why a higher percentage of patients switched off of Avastin than Lucentis (23% vs. 3% initially treated with Lucentis); however, the author offers only a limited explanation of this occurrence stating, 'the availability of ranibizumab most likely accounted for some of the changes observed in the bevacizumab group.'"

IN BRIEF

■ **VEGF Trap a future gold standard therapy?** In a survey of 91 US and European retina specialists, Regeneron/Bayer's as yet unapproved aflibercept (VEGF Trap-Eye) was named as a therapy for wet AMD that has the potential to reach gold-standard status. VEGF Trap-Eye is currently completing its pivotal phase 3 trials.

Decision Resources, a leading research and advisory firm for pharmaceutical and healthcare issues, reported that both Genentech's Lucentis and Regeneron/Bayer's VEGF Trap-Eye can be expected to earn Decision Resources' proprietary clinical gold standard status for wet AMD in 2013 and 2018.

A unique future gold standard cannot be identified because neither thought-leader opinion nor available clinical data can show that VEGF Trap-Eye has any advantages or disadvantages relative to Lucentis in terms of efficacy, safety and tolerability or delivery attributes.

However, Decision Resources believes that are still unmet medical needs in the treatment of wet AMD.

■ **Lux files for uveitis drug approval**. Lux Biosciences, Inc. has submitted regulatory filings to both the FDA and European Medicines Agency (EMA) seeking marketing approval for its investigational drug Luveniq (LX211) oral voclosporin for the treatment of noninfectious uveitis involving the intermediate or posterior segments of the eye.

Lux said efficacy of LX211 was demonstrated in two controlled, randomized, multicenter trials including data from 450 patients at 56 sites in seven countries. The safety data include a total of 2,110 subjects who received voclosporin during its clinical development in uveitis and psoriasis, about 500 of whom were treated for more than 36 weeks and about 200 for more than 52 weeks.

LX211 had previously received orphan drug status from the FDA and EMA, and fast-track status from the FDA. Based on the latter, Lux Biosciences has requested priority review from the FDA.

■ **Wnt pathway plays role in DR**. Scientists have identified a molecular pathway that appears to play a vital role in diabetic retinopathy. In a study appearing in the *American Journal of Pathology*, researchers show that retinal levels and nuclear translocation of beta-catenin, a key effector in the canonical Wnt pathway, were increased in humans with DR and in three DR models. Retinal levels of low-density lipoprotein receptor-related proteins 5 and 6, coreceptors of Wnts, were also elevated in the DR models.

The high glucose-induced activation of beta-catenin was attenuated by aminoguanidine, suggesting that oxidative stress is a direct cause for the Wnt pathway activation in diabetes. Indeed, Dickkopf homolog 1, a specific inhibitor of the Wnt pathway, ameliorated retinal inflammation, vascular leakage, and retinal neovascularization in the DR models. Dickkopf homolog 1 also blocked the generation of reactive oxygen species induced by high glucose, suggesting that Wnt signaling contributes to the oxidative stress in diabetes. This indicates that the Wnt pathway plays a pathogenic role in DR and represents a novel therapeutic target. **RP**

ERRATUM

In the article "Short-pulse Laser Treatment: Redefining Retinal Therapy," in the January/February 2010 issue of *Retinal Physician*, Figure 1 was mislabeled. The image is not of a rabbit eye, but of a human eye. *Retinal Physician* regrets the error.

Retinal Physician, Issue: March 2010

REGENERON
science to medicine®

December 20, 2010

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)

In Phase 3 study in CRVO, 56 percent of VEGF Trap-Eye patients gained at least 15 letters of vision compared to 12 percent in control group; VEGF Trap-Eye patients on average gained 17 letters of vision compared to mean loss of 4 letters in control group

In Phase 2 study in DME, patients in all VEGF Trap-Eye dose groups, including VEGF Trap-Eye dosed every two months, maintained or increased vision gains through 52-weeks

Regeneron to receive $20 million in milestone payments in connection with VEGF Trap-Eye program

Tarrytown, NY, USA, and Berlin, Germany, December 20, 2010 -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Bayer HealthCare today announced positive top-line results for VEGF Trap-Eye (aflibercept ophthalmic solution) in the COPERNICUS study, which is led by Regeneron, the first of two Phase 3 studies in patients with macular edema due to central retinal vein occlusion (CRVO). In this trial, 56.1 percent of patients receiving VEGF Trap-Eye 2 milligrams (mg) monthly gained at least 15 letters of vision from baseline, compared to 12.3 percent of patients receiving sham injections ($p<0.0001$), the primary endpoint of the study. Patients receiving VEGF Trap-Eye 2mg monthly gained, on average, 17.3 letters of vision compared to a mean loss of 4.0 letters with sham injections ($p<0.001$), a secondary endpoint. The second Phase 3 study, GALILEO, is currently ongoing and is led by Bayer HealthCare.

VEGF Trap-Eye was generally well tolerated and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. A total of 114 patients were randomized to receive VEGF Trap-Eye and 73 patients to the control arm. Serious ocular adverse events in the VEGF Trap-Eye group were uncommon (3.5%) and were more frequent in the control group (13.5%). The incidence of non-ocular serious adverse events was generally well-balanced between the treatment arms. There were no deaths among the 114 patients treated with VEGF Trap-Eye and two in the 73 (2.7%) patients treated with sham injections.

"In the COPERNICUS trial, patients treated with VEGF Trap-Eye experienced a marked improvement in vision," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "If these results are confirmed by data from the GALILEO study, expected in the second quarter of 2011, VEGF Trap-Eye could provide patients and physicians with a new treatment option for central retinal vein occlusion."

"After reporting positive results from our global Phase 3 program (VIEW 1 and VIEW 2 studies) for the treatment of the neovascular form of age related macular degeneration (wet AMD), we are pleased to also have a positive Phase 3 trial with VEGF Trap-Eye in central retinal vein occlusion, a potential second indication," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "We are working diligently with Regeneron to prepare regulatory filings for VEGF Trap-Eye in wet AMD to submit in the first half of 2011."

Detailed results for COPERNICUS will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

Regeneron will receive a $10 million milestone payment from Bayer HealthCare in connection with the COPERNICUS trial meeting its primary endpoint and received a $10 million milestone payment in December 2010 for the positive VIEW 1 and VIEW 2 trial results in wet AMD.

Phase 2 DME Results
Regeneron and Bayer HealthCare also reported 52 week follow-up results from the Phase 2 DA VINCI study in patients with diabetic macular edema (DME). In this study, the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month. Based on these positive results, Regeneron and Bayer HealthCare are discussing plans to initiate Phase 3 studies.

In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled **DA VINCI** (**D**ME **A**nd **V**EGF Trap-Eye: **IN**vestigation of **C**linical Impact), 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. Two groups

received monthly doses of 0.5 or 2mg of VEGF Trap-Eye throughout the 12-month dosing period. Two groups received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing or PRN (as-needed) dosing with very strict repeat dosing criteria. Mean gains in visual acuity versus baseline were as follows:

	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline[1] (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**

*Following 3 initial monthly doses
**p<0.01 versus laser
[1] Primary endpoint

No significant differences among the VEGF Trap-Eye arms were observed. Approximately 80 percent of the VEGF Trap-Eye patients and 75 percent of the laser patients remained in the study through 52 weeks.

VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study.* The most common adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent ocular adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, ocular redness (hyperemia), and increased intraocular pressure. The incidence of non-ocular serious adverse events was generally well balanced between all treatment arms. There were six deaths (3.4%) among the 175 patients treated with VEGF Trap-Eye and one (2.3%) in the 44 patients treated with laser over 12 months. Detailed results for DA VINCI will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

About the Phase 3 CRVO Program
Patients in the COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) and the identical GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) studies receive six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. Patients in the COPERNICUS trial were randomized in a 3:2 ratio with 114 patients randomized to receive VEGF Trap-Eye and 73 randomized to the control arm. At the end of the initial six months, all patients randomized to VEGF Trap-Eye are dosed on a PRN (as needed) basis for another six months. In the COPERNICUS trial, patients randomized to sham injections in the first six months are eligible to cross over to VEGF Trap-Eye PRN dosing in the second six months. During the second six months of the studies, all patients are eligible for rescue laser treatment. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity.

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

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

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

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

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO), and other eye diseases and disorders. In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval for the treatment of wet AMD in Europe and the U.S. in the first-half of 2011.

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

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

About Bayer HealthCare
The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

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

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

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*As noted during our investor teleconference on December 20, 2010, the press release inadvertently omitted certain information, which

Regeneron does not consider to be material. To reflect inclusion of such omitted information, this sentence would be replaced with the following: "In this study, VEGF Trap-Eye was generally well-tolerated and no patients experienced ocular drug-related serious adverse events. With respect to the number of patients with non-ocular serious adverse events judged by investigators to be drug-related, there were none during the first six months of the study and one in the second six months."

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OBS 8

REGENERON
science to medicine®

May 1, 2008

Regeneron Reports First Quarter 2008 Financial and Operating Results

TARRYTOWN, N.Y., May 01, 2008 (BUSINESS WIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced financial and operating results for the first quarter 2008. The Company reported a net loss of $11.6 million, or $0.15 per share (basic and diluted), for the first quarter of 2008 compared with a net loss of $29.9 million, or $0.46 per share (basic and diluted), for the first quarter of 2007.

At March 31, 2008, cash, restricted cash, and marketable securities totaled $827.9 million compared with $846.3 million at December 31, 2007. The Company's $200.0 million of convertible notes, which bear interest at 5.5 percent per annum, mature in October 2008.

Current Business Highlights

ARCALYST™ (rilonacept) - Inflammatory Diseases

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

A Phase 2 safety and efficacy trial of ARCALYST is underway in the prevention of gout flares induced by the initiation of uric acid-lowering drug therapy used to control gout. The Company is also evaluating the potential use of ARCALYST in other indications in which interleukin-1 (IL-1) may play a role.

Aflibercept (VEGF Trap) - Oncology

In their collaboration to develop aflibercept for the treatment of cancer, Regeneron and sanofi-aventis currently are enrolling patients in four Phase 3 trials that combine aflibercept with standard chemotherapy regimens. One trial is evaluating aflibercept as a 2nd line treatment for metastatic colorectal cancer in combination with folinic acid, 5-FU, and irinotecan. A second trial is evaluating aflibercept as a 1st line treatment for metastatic pancreatic cancer in combination with gemcitabine. A third trial is evaluating aflibercept as a 1st line treatment for metastatic androgen independent prostate cancer in combination with docetaxel/prednisone. The fourth trial is evaluating aflibercept as a 2nd line treatment for metastatic non-small cell lung cancer in combination with docetaxel. All four trials are studying the current standard of chemotherapy care for the cancer being studied with and without aflibercept. In addition, more than 13 studies are being conducted in conjunction with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) evaluating aflibercept as a single agent or in combination with chemotherapy regimens in a variety of cancer indications.

VEGF Trap-Eye - Eye Diseases

VEGF Trap-Eye is a specially purified and formulated form of the VEGF Trap for use in intraocular applications. Regeneron and Bayer HealthCare initiated a Phase 3 global development program of VEGF Trap-Eye in the neovascular form of Age-related Macular Degeneration (wet AMD) in the third quarter of 2007. The first trial, known as VIEW 1 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), is comparing VEGF Trap-Eye and ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.), an anti-angiogenic agent approved for use in wet AMD. The trial is evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye, compared with ranibizumab dosed every four weeks according to its label. Bayer HealthCare is initiating a second Phase 3 trial of VEGF Trap-Eye in wet AMD in the European Union and other parts of the world outside the U.S.

In April 2008, Regeneron and Bayer HealthCare announced the 32-week endpoint results of a Phase 2 study evaluating VEGF Trap-Eye in wet AMD, which were presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, Florida. The analysis showed that VEGF Trap-Eye dosed on a PRN (as-needed) dosing schedule maintained the statistically significant gain in visual acuity achieved after an initial 12-week, fixed-dosing phase.

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

Patients receiving monthly doses of VEGF Trap-Eye, either 0.5 or 2.0 mg, for 12 weeks followed by PRN dosing thereafter achieved mean improvements in visual acuity of 8.0 (p less than0.01 versus baseline) and 10.1 letters (p less than 0.0001 versus baseline), respectively, and mean decreases in retinal thickness of 141 (p less than 0.0001 versus baseline) and 162 microns (p less than 0.0001 versus baseline) at week 32, respectively.

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

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

Monoclonal Antibodies

Regeneron and sanofi-aventis are collaborating on the discovery, development, and commercialization of fully human monoclonal antibodies generated by Regeneron using its VelocImmune® technology. The first therapeutic antibody to enter clinical development under the collaboration is REGN88, an antibody to the interleukin-6 receptor (IL-6R) that is being evaluated in rheumatoid arthritis. A second antibody candidate, an antibody to Delta-like ligand-4 (Dll4), is slated to start clinical development in mid-2008. The Company and sanofi-aventis plan to advance two to three new antibodies into clinical development each year.

Financial Results

Revenue

Regeneron's total revenue increased to $56.4 million in the first quarter of 2008 from $15.8 million in the same period of 2007. Contract research and development revenue in the first quarter of 2008 principally related to the Company's aflibercept and antibody collaborations with sanofi-aventis and the Company's VEGF Trap-Eye collaboration with Bayer HealthCare. In the first quarter of 2007, contract research and development revenue primarily related to the Company's aflibercept collaboration with sanofi-aventis. Technology licensing revenue related to the Company's license agreements with AstraZeneca and Astellas.

Regeneron recognized contract research and development revenue of $13.8 million in the first quarter of 2008 related to the Company's aflibercept collaboration with sanofi-aventis, compared with $11.8 million in the same period of 2007. Contract research and development revenue from the collaboration consisted of reimbursement of aflibercept development expenses incurred by the Company plus recognition of amounts related to $105.0 million of previously received and deferred non-refundable, up-front payments. Reimbursement of expenses increased to $11.7 million in the first quarter of 2008 from $9.6 million in the same period of 2007, principally due to higher costs related to the Company's manufacture of aflibercept clinical supplies and higher clinical development costs. With respect to the $105.0 million of up-front payments from sanofi-aventis, $2.1 million was recognized in the first quarter of 2008 compared to $2.2 million in the same period of 2007.

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

Regeneron recognized contract research and development revenue of $21.9 million in the first quarter of 2008 related to the Company's antibody collaboration with sanofi-aventis. Contract research and development revenue from the antibody collaboration consisted of $15.1 million for reimbursement of the Company's expenses under the collaboration's discovery agreement, $4.2 million for reimbursement of the Company's REGN88 development expenses, and $2.6 million related to an $85.0 million non-refundable, up-front payment, which was deferred upon receipt in December 2007.

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

In the first quarter of 2008, the Company recorded $9.0 million of contract research and development revenue from Bayer HealthCare, consisting of $3.3 million related to the $75.0 million up-front licensing payment and the $20.0 million milestone payment and $5.7 million related to the portion of the Company's first quarter 2008 VEGF Trap-Eye development expenses that is reimbursable from Bayer HealthCare.

Regeneron has entered into non-exclusive license agreements with AstraZeneca and Astellas that allow those companies to utilize VelocImmune® technology in their internal research programs to discover human monoclonal antibodies. Each company made a $20.0 million up-front, non-refundable payment in 2007 and will make up to five additional annual payments of $20.0 million, subject to the ability to terminate their agreements after making three additional payments. Upon receipt, these payments are deferred and are recognized as revenue ratably over approximately the ensuing year of each agreement. Regeneron will also receive a mid-single-digit royalty on sales of any antibodies discovered utilizing VelocImmune. In the first quarter of 2008 and 2007, the Company recognized $10.0 million and $2.1 million, respectively, of technology licensing revenue related to these agreements.

ARCALYST™ (rilonacept) Product Sales

In late March 2008, the Company shipped $0.8 million of ARCALYST to its distributors, which was fully deferred at March 31, 2008 and classified as deferred revenue in the Company's financial statements.

Expenses

Total operating expenses for the first quarter of 2008 were $72.3 million, 46 percent higher than the same period in 2007. Our average headcount increased to 714 in the first quarter of 2008 from 585 in the same period of 2007 primarily as a result of our expanding research and development activities directed toward preclinical and clinical development of product candidates, including ARCALYST™, aflibercept, VEGF Trap-Eye, and monoclonal antibodies (including REGN88 and the Dll4 antibody).

Operating expenses included non-cash compensation expense related to employee stock option and restricted stock awards of $8.3 million and $6.6 million in the first quarters of 2008 and 2007, respectively.

Research and development (R&D) expenses increased to $61.3 million in the first quarter of 2008 from $41.2 million in the comparable quarter of 2007. The Company incurred higher R&D costs primarily related to additional R&D headcount, clinical development costs for VEGF Trap-Eye and ARCALYST, and costs related to manufacturing supplies of aflibercept, VEGF Trap-Eye, and the Dll4 antibody.

Selling, general, and administrative expenses increased to $11.0 million in the first quarter of 2008 from $8.2 million in the comparable period of 2007. In the first quarter of 2008, the Company incurred costs associated with the launch of ARCALYST. In addition, the Company incurred higher compensation expense and recruitment costs associated with expanding the Company's headcount, and higher legal fees related to general corporate matters.

Other Income

Investment income increased to $7.3 million in the first quarter of 2008 from $6.7 million in the comparable quarter of 2007. The increase in investment income resulted primarily from higher balances of cash and marketable securities, due primarily to receipts from sanofi-aventis of $312.0 million for the purchase of 12 million shares of the Company's Common Stock in December 2007 and the $85.0 million up-front payment related to the antibody collaboration, partially offset by lower effective interest rates in 2008.

About Regeneron Pharmaceuticals

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

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

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

	March 31, 2008	December 31, 2007
ASSETS		
Cash, restricted cash, and marketable securities	$827,858	$846,279
Receivables	32,960	18,320
Property, plant, and equipment, net	58,419	58,304
Other assets	11,639	13,355
Total assets	$930,876	$936,258
LIABILITIES AND STOCKHOLDERS' EQUITY		
Accounts payable and accrued expenses	$30,314	$39,232
Deferred revenue	239,959	236,759
Notes payable	200,000	200,000
Stockholders' equity	460,603	460,267
Total liabilities and stockholders' equity	$930,876	$936,258

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

	For the three months ended March 31, 2008	2007
Revenues		
Contract research and development	$46,383	$13,645

Technology licensing	10,000	2,143
	56,383	15,788
Expenses		
Research and development	61,270	41,235
Selling, general, and administrative	11,024	8,202
	72,294	49,437
Loss from operations	(15,911)	(33,649)
Other income (expense)		
Investment income	7,304	6,743
Interest expense	(3,011)	(3,011)
	4,293	3,732
Net loss	$(11,618)	$(29,917)
Net loss per share amounts, basic and diluted	$(0.15)	$(0.46)
Weighted average shares outstanding, basic and diluted	78,493	65,563

SOURCE: Regeneron Pharmaceuticals, Inc.

Regeneron Pharmaceuticals, Inc.
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Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Date
13.09.2016

Reference	Application No./Patent No.
	12700590.8 - 1466 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Acknowledgment of receipt of observations by third parties (Article 115 EPC)

Receipt of your letter dated 07.09.2016 is hereby acknowledged.

Under Article 115 EPC you will not be a party to the proceedings before the European Patent Office.

☐ In your letter the following documents are mentioned which were not enclosed, and which are not available in the EPO:

☐ The third party observations have not been filed in an official language of the EPO (R. 114(1) EPC).

You are requested to file copy(ies) and/or translation(s) in one of the official EPO languages within **two months** of notification of this communication if they are to be taken into account.

For the Examining Division

Third Party Observation for application Number EP20120700590

Successful submission of observation took place on 16/11/2016 17:02

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
Publication Number: EP2663325
Applicant: REGENERON PHARMA[US]
Date of publication: 20.11.2013
Date of filing: 11.01.2012

These observations have been filed by:

Anonymous

1. Facts and evidence

1.1. Reference is made to the following documents

PL1

1.2. Observations concerning the public availability of the non-patent literature

NPL1

2. Prior Use

2.1. Prior use (1)

When did the prior use occur?

What was made available?

Where was it made available?

How and to whom was it made available?

3. Common General Knowledge

4. Novelty (Article 54 EPC)

4.1. Novelty (1)

5. Inventive step (Article 56 EPC)

5.1. Inventive step (1)

Features known from the prior art:

Novel features not known from the prior art:

The technical effect caused or technical problems solved by the novel features:

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

6. Any further Observations, e.g. Articles 52(2), 53, 57, 76, 83, 84, 123(2) EPC, validity of the priority date

6.1. Unallowable amendments (Articles 76 and 123 EPC)

6.2. Sufficiency of disclosure (Article 83 EPC)

6.3. Clarity (Article 83 EPC)

6.4. Futher observations

The TPO filed 7 September 2016 was not properly served to the applicant. In fact the observation letter served with the three Annexes of the TPO of 7 September was the one of the anonymous TPO of 5 September 2016.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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ROYAUME UNI

Date
01.12.2016

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Corrected version (1)

Communication pursuant to Rule 114(2) EPC

Please find enclosed observations by a third party concerning the patentability of the invention of the above-mentioned patent application. That person is not a party to the proceedings before the EPO (Art. 115 EPC).

Under Rule 114(2) EPC you may comment on the observations.

For the Examining Division

(1) replace our letter dated 13.09.2016 -The observiation letter of the Observation by Third Party filed on 07.09.2016 was not properly served to the applicant. In fact the observation letter served with the 3 annexes of 07.09.2016 was the one of the anonymous observation filed on 05.12.2016

Maiwald

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Kooperation mit

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GF (Geschäftsführer), C (Counsel), PA (Patentanwalt), EPA (European Patent Attorney), RA (Rechtsanwalt für gewerblichen Rechtsschutz)
MUC (München), DUS (Düsseldorf)
* Zulassung ruht

Europäisches Patentamt

80298 München

Munich, 7 September 2016

Application No.: EP 12 700 590.8
Applicant: Regeneron Pharmaceuticals, Inc.

Our ref.: 9281-TPO / RN

Observations pursuant to Article 115 EPC regarding European patent application 12 700 590.8

In accordance with Article 115 EPC, Third Party Observations against European patent application EP 12 700 590.8 (EP 2 663 325 A1) are filed on behalf of

bioeq GmbH
Tölzer Straße 12
83607 Holzkirchen
Germany

For the reasons set forth below, the presently pending claims of said application are **not in compliance with the requirements of the EPC**.

RN:LA

I. Prior art

The following documents disclosing the subject-matter of the pending claims as filed on 17 December 2014 are provided:

Annex 1	Press Release of Regeneron dated 22 November 2010
Annex 2	Press Release of Regeneron dated 20 December 2010
Annex 3	Article in Retinal Physician (March 2010)

All documents were published before the earliest priority date of 13 January 2011 and are therefore prior art according to Article 54(2) EPC.

II. The European patent application EP 2 663 325 A1

1. Bibliographical data

Earliest priority date:	13 January 2011
Filing date:	11 January 2012
Latest expiry date (if granted):	11 January 2032
Designated contracting states:	AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR
Applicant:	Regeneron Pharmaceuticals, Inc.
Current state:	Examination is in progress

2. Status

The European patent application is currently undergoing examination.

The first office action of the Examining Division according to Article 94(3) EPC was issued on 21 August 2014 and raised objections under Article 84 and 83 EPC (lack of clarity and sufficiency of disclosure) and Article 56 EPC (lack of inventive step).

Applicant filed a reply including amended claims on 17 December 2014.

3. Claims

Pending claim 1 of EP 2 663 325 A1 filed with the reply on 17 December 2014 is directed to:

> *"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 two 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 4 weeks after the immediately preceding dose;*
> *wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1."*

Pending claims 2 to 6 specify the angiogenic eye disorder as age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, and corneal neovascularization, respectively.

Pending claim 7 specifies the VEGF antagonist to comprise (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.

Pending claims 8 to 10 specify the route of administration as topical or intraocular administration, intraocular administration, or intravitreal administration, respectively.

Pending claims 11 and 12 specify that all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist, and 0.5 mg or 2 mg of the VEGF antagonist, respectively.

It is noted that a press article of Regeneron published on 28 September 2008 was cited by the Examining Division (ED) in its communication dated 21 August 2014 as document D13. This document relates to the results of the phase II study preceding VIEW-1 and VIEW-2 studies and mentions the VIEW studies and dosage regimens to be administered therein. However, according to the ED, since no results of the phase III study are presented, the disclosure is not enabled. The ED further noted that the results of the phase III study are presented in example 4 of EP 2 663 325.

However, this reasoning means that any document disclosing the results of the phase III clinical studies in which the claimed dosage regimen is used anticipates the subject-matter of pending claim 1.

The following discussion will show that at the earliest priority date the results of phase III clinical studies using the claimed dosage regimen showing a therapeutic effect had already been published.

3. Lack of novelty (Article 54 EPC)

3.1 Press release of Regeneron dated 22 November 2010 (Annex 1)

Regeneron published a press release summarising the results of the VIEW-1 and VIEW-2 studies on 22 November 2010, i.e. before the priority date.

Annex 1 discloses that VEGF Trap-Eye was administered every two months after three monthly loading doses (second page, third paragraph):

> *"In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5mg monthly, 2mg monthly, or 2mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5mg every month during the first year of the studies."* (emphasis added)

In this context, the 2 mg aflibercept dose administered in the first visit corresponds to the single initial dose of the claimed VEGF antagonist, the 2 mg aflibercept doses administered at weeks 4 and 8 correspond to two secondary doses of the claimed VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose, and the 2 mg aflibercept doses administered thereafter every 8 weeks correspond to the tertiary doses of the claimed VEGF antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline).

VEGF Trap-Eye is aflibercept ophthalmic solution (see first page, first paragraph of Annex I). According to paragraph [0007] of WO 2012/097019 A1

aflibercept is the same molecule as VEGFR1R2-FcΔC1(a) to which claim 1 refers.

According to Annex 1 the results of the VIEW studies show that *"all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month."* (cf. first page, first paragraph; emphasis added). This shows that a therapeutic effect is indeed obtained by treatment with a dosage regimen as required by the pending claims.

Further, Table 1 presented in Example 4 of EP 2 663 325 A1 is already shown on page 2 of Annex 1.

Thus, Annex 1 discloses all features of pending claims 1, 2 and 7 to 12.

3.2 Press release of Regeneron dated 20 December 2010 (Annex 2)

Regeneron published a further press release relating to the results of the studies COPERNICUS and DA VINCI on 20 December 2010, i.e. before the earliest priority date.

DA VINCI is a phase II study in patients with diabetic macular edema. In this study participants were randomized into one of five groups: one group receiving laser treatment (control group), two groups receiving 0.5 or 2 mg of VEGF Trap-Eye monthly, and two groups receiving three initial monthly doses of 2 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing (corresponding to the regimen defined in pending claim 1) or as-needed dosing (first page, penultimate paragraph).

Annex 2 reports that *"the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the [DA VINCI] study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month."* (cf. first page, penultimate paragraph; emphasis added).

Furthermore, Table 2 presented in Example 5 of EP 2 663 325 A1 is already shown on page 2 of Annex 2.

Thus, Annex 2 discloses all features of pending claims 1, 4 and 7 to 12.

3.3 Article in Retinal Physician (March 2010) (Annex 3)

A brief news article relating to the DA VINCI study and interim results thereof was published in the March 2010 issue of Retinal Physician and is available on the homepage (http://www.retinalphysician.com/printarticle.aspx?articleID=104007).

Annex 3 discloses the dosing groups in the last paragraph of the article "VEGF Trap Has Positive DME Data" (on page 2/4), including two groups receiving three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline, weeks 4 and 8), followed through 24 weeks by either dosing every 8 weeks (corresponding to the regimen defined in pending claim 1) or as-needed dosing.

Annex 3 further describes that the DA VINCI study showed positive interim results (first paragraph of the article) and that each one of the dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean

improvements in visual acuity compared to patients receiving laser therapy (penultimate paragraph of the article).

Thus, Annex 3 also discloses all features of pending claims 1, 4 and 7 to 12.

III. Conclusion

Results from phase III clinical studies showing the successful use of the dosage regimen of pending claim 1 were published before the priority date of EP 2 663 325 A1. The subject-matter of pending claim 1 is therefore not novel.

The same is true for the subject-matter of pending claims 2, 4 and 7 to 12.

Pending claims 3, 5 and 6 relating to different angiogenic eye disorders are considered to be obvious in view of the results of the cited studies.

Thus, in view of the published results all pending claims do not meet the requirements of the EPC.

Maiwald Patentanwalts GmbH
(Andrea Lasar)

Encls.
Annex 1-3

REGENERON
science to medicine®

November 22, 2010

Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration

In both studies, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, achieved primary endpoint compared to ranibizumab dosed every month
Regulatory applications for marketing approval planned in first-half of 2011

TARRYTOWN, N.Y. and BERLIN, Nov. 22, 2010 /PRNewswire-FirstCall/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare today announced that in two parallel Phase 3 studies in patients with the neovascular form of age-related macular degeneration (wet AMD), all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab.

Further results will be presented at the Angiogenesis Conference in February 2011. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval in Europe and the U.S. in the first-half of 2011 based on the positive results of the VIEW 1 and VIEW 2 trials.

In the North American VIEW 1 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 95 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 95 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. In the international VIEW 2 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 96 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 96 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart.

"The currently available anti-VEGF therapies have significantly advanced the treatment of wet AMD, actually improving vision in many patients. However, monthly injections are required to optimize and maintain vision gain over the long-term," said Ursula Schmidt-Erfurth, M.D., Professor and Chair of the Department of Ophthalmology at the University Eye Hospital in Vienna, Austria and the VIEW 2 Principal Investigator. "The results of the VIEW studies indicate that VEGF Trap-Eye could establish a new treatment paradigm for the management of patients with wet AMD --- predictable every-other-month dosing without the need for intervening monitoring or dosing visits."

"In an effort to avoid the inconvenience of monthly office visits and the burden of monthly injections into the eye for their wet AMD patients, retinal specialists have tried to extend the benefits of the existing anti-VEGF therapy with less frequent dosing. A growing body of data suggests that this practice may result in inconsistent visual acuity outcomes," said Jeffrey Heier, M.D., a clinical ophthalmologist and retinal specialist at Ophthalmic Consultants of Boston, Assistant Professor of ophthalmology at Tufts School of Medicine, and Chair of the Steering Committee for the VIEW 1 trial. "A critical goal of these studies was to demonstrate that VEGF Trap-Eye could achieve robust improvements in vision and maintain them over time with a more convenient every-other-month dose. Achievement of this goal could be important for patients, care givers, and physicians."

In the VIEW 1 study, patients receiving VEGF Trap-Eye 2mg monthly achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly; patients receiving VEGF Trap-Eye 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 VEGF Trap-Eye in the VIEW 1 study and all dose groups in the VIEW 2 study were not statistically different from ranibizumab in this secondary endpoint.

A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation,

breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

In the second year of the studies, patients in VIEW 1 and VIEW 2 will continue to be treated with the same dose per injection as in the first year but administered only every three months, or more often for any worsening of AMD, based on protocol-defined criteria (called "quarterly capped PRN" dosing).

About the VIEW Program

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

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

The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain visual acuity at the end of one year, compared to ranibizumab patients. Visual acuity is measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.

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

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

*Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart
**Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)
*** Test for superiority
NS=non-significant

About Wet AMD

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

About VEGF Trap-Eye

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

VEGF Trap-Eye is also in Phase 3 development for the treatment of Central Retinal Vein Occlusion (CRVO), another major cause of blindness, in two identical studies. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron and the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. Initial data from the CRVO program are anticipated in early 2011.

VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). In February 2010, Regeneron and Bayer HealthCare announced that treatment with VEGF Trap-Eye in the Phase 2 DA VINCI (DME And VEGF Trap-Eye: INvestigation of Clinical Impact) study demonstrated a statistically significant improvement in visual acuity versus baseline after six months of treatment compared to focal laser therapy, the primary endpoint of the study. Initial one-year results from this trial will be available before the end of this year.

About Regeneron Pharmaceuticals

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

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward Looking Statement

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

Bayer Forward-Looking Statements

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

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SOURCE Regeneron Pharmaceuticals, Inc.

REGENERON
science to medicine®

December 20, 2010

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)

In Phase 3 study in CRVO, 56 percent of VEGF Trap-Eye patients gained at least 15 letters of vision compared to 12 percent in control group; VEGF Trap-Eye patients on average gained 17 letters of vision compared to mean loss of 4 letters in control group

In Phase 2 study in DME, patients in all VEGF Trap-Eye dose groups, including VEGF Trap-Eye dosed every two months, maintained or increased vision gains through 52-weeks

Regeneron to receive $20 million in milestone payments in connection with VEGF Trap-Eye program

Tarrytown, NY, USA, and Berlin, Germany, December 20, 2010 -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Bayer HealthCare today announced positive top-line results for VEGF Trap-Eye (aflibercept ophthalmic solution) in the COPERNICUS study, which is led by Regeneron, the first of two Phase 3 studies in patients with macular edema due to central retinal vein occlusion (CRVO). In this trial, 56.1 percent of patients receiving VEGF Trap-Eye 2 milligrams (mg) monthly gained at least 15 letters of vision from baseline, compared to 12.3 percent of patients receiving sham injections ($p<0.0001$), the primary endpoint of the study. Patients receiving VEGF Trap-Eye 2mg monthly gained, on average, 17.3 letters of vision compared to a mean loss of 4.0 letters with sham injections ($p<0.001$), a secondary endpoint. The second Phase 3 study, GALILEO, is currently ongoing and is led by Bayer HealthCare.

VEGF Trap-Eye was generally well tolerated and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. A total of 114 patients were randomized to receive VEGF Trap-Eye and 73 patients to the control arm. Serious ocular adverse events in the VEGF Trap-Eye group were uncommon (3.5%) and were more frequent in the control group (13.5%). The incidence of non-ocular serious adverse events was generally well-balanced between the treatment arms. There were no deaths among the 114 patients treated with VEGF Trap-Eye and two in the 73 (2.7%) patients treated with sham injections.

"In the COPERNICUS trial, patients treated with VEGF Trap-Eye experienced a marked improvement in vision," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "If these results are confirmed by data from the GALILEO study, expected in the second quarter of 2011, VEGF Trap-Eye could provide patients and physicians with a new treatment option for central retinal vein occlusion."

"After reporting positive results from our global Phase 3 program (VIEW 1 and VIEW 2 studies) for the treatment of the neovascular form of age related macular degeneration (wet AMD), we are pleased to also have a positive Phase 3 trial with VEGF Trap-Eye in central retinal vein occlusion, a potential second indication," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "We are working diligently with Regeneron to prepare regulatory filings for VEGF Trap-Eye in wet AMD to submit in the first half of 2011."

Detailed results for COPERNICUS will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

Regeneron will receive a $10 million milestone payment from Bayer HealthCare in connection with the COPERNICUS trial meeting its primary endpoint and received a $10 million milestone payment in December 2010 for the positive VIEW 1 and VIEW 2 trial results in wet AMD.

Phase 2 DME Results
Regeneron and Bayer HealthCare also reported 52 week follow-up results from the Phase 2 DA VINCI study in patients with diabetic macular edema (DME). In this study, the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month. Based on these positive results, Regeneron and Bayer HealthCare are discussing plans to initiate Phase 3 studies.

In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled **DA VINCI** (**D**ME **A**nd **V**EGF Trap-Eye: **IN**vestigation of **C**linical Impact), 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. Two groups

received monthly doses of 0.5 or 2mg of VEGF Trap-Eye throughout the 12-month dosing period. Two groups received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing or PRN (as-needed) dosing with very strict repeat dosing criteria. Mean gains in visual acuity versus baseline were as follows:

	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline[1] (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**

*Following 3 initial monthly doses
**p<0.01 versus laser
[1] Primary endpoint

No significant differences among the VEGF Trap-Eye arms were observed. Approximately 80 percent of the VEGF Trap-Eye patients and 75 percent of the laser patients remained in the study through 52 weeks.

VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study.* The most common adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent ocular adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, ocular redness (hyperemia), and increased intraocular pressure. The incidence of non-ocular serious adverse events was generally well balanced between all treatment arms. There were six deaths (3.4%) among the 175 patients treated with VEGF Trap-Eye and one (2.3%) in the 44 patients treated with laser over 12 months. Detailed results for DA VINCI will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

About the Phase 3 CRVO Program
Patients in the COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) and the identical GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) studies receive six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. Patients in the COPERNICUS trial were randomized in a 3:2 ratio with 114 patients randomized to receive VEGF Trap-Eye and 73 randomized to the control arm. At the end of the initial six months, all patients randomized to VEGF Trap-Eye are dosed on a PRN (as needed) basis for another six months. In the COPERNICUS trial, patients randomized to sham injections in the first six months are eligible to cross over to VEGF Trap-Eye PRN dosing in the second six months. During the second six months of the studies, all patients are eligible for rescue laser treatment. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity.

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

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

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

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

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO), and other eye diseases and disorders. In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval for the treatment of wet AMD in Europe and the U.S. in the first-half of 2011.

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

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

About Bayer HealthCare
The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

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

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*As noted during our investor teleconference on December 20, 2010, the press release inadvertently omitted certain information, which

Regeneron does not consider to be material. To reflect inclusion of such omitted information, this sentence would be replaced with the following: "In this study, VEGF Trap-Eye was generally well-tolerated and no patients experienced ocular drug-related serious adverse events. With respect to the number of patients with non-ocular serious adverse events judged by investigators to be drug-related, there were none during the first six months of the study and one in the second six months."

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ANNEX 3

Article Date: 3/1/2010

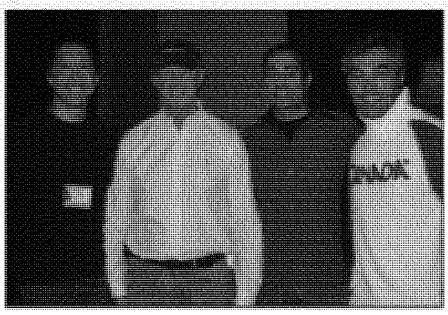
SUBSPECIALTY NEWS

Fellows Forum Marks 10th Year

Dr. Steve Charles is Guest Lecturer.

■ The tenth annual Retina Fellows' Forum took place on Jan. 29 and 30 at the Westin River North in frigid Chicago. Eighty North American fellows participated in an educational and social program that has become a much-anticipated fixture of the final year of vitreoretinal training.

As in past years, the fellows spent considerable time in the lecture hall with a panel of volunteer faculty, led by Course Director David Chow, MD, and co-directors Carl Awh, MD, and Tarek Hassan, MD. Ophthalmologists Dean Eliott, Phil Ferrone, Jeff Heier, Nancy Holekamp and Peter Kaiser completed the faculty.



From left, Drs. Carl Awh, Steve Charles (Distinguished Guest Lecturer), Tarek Hassan and David Chow.

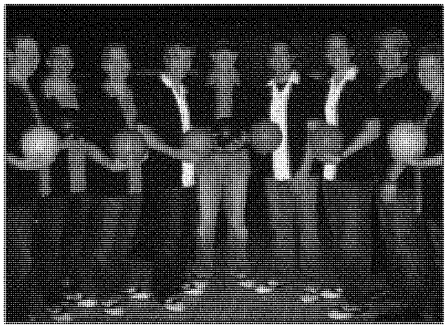
The meeting began on Friday evening with an AMD Symposium and sessions on Diagnostic Instrumentation and Pediatric Retina. New to the meeting were the inaugural "Faculty Debates," in which the faculty debated the following topics: Avastin vs. Lucentis; Pneumatic Retinopexy vs. Scleral Buckle vs. Vitrectomy, and Fluorescein Angiography vs. OCT. Topics were assigned to the faculty, who relied upon clinical data, personal experience, and (most effectively) humor to defend their positions.

A Friday evening reception and dinner provided the first opportunity for the "graduating class" of 2010 fellows to socialize with their peers, the faculty, and representatives from industry.

Saturday offered a full day of panel-driven discussions on Diabetic Retinopathy, Retinal Vascular Occlusion, Medical and Surgical "Pearls," "News You Can Use," and advice on career and lifestyle management. As always, a highlight of the meeting was the Distinguished Guest Lecture, this year delivered by Steve Charles, MD. Dr. Charles captivated and inspired the audience with his talk on "Technology, Technique, and the Pursuit of Happiness."

For the 10th consecutive year, Bausch & Lomb provided essential support as the major sponsor of the Retina Fellows' Forum. Genentech provided a generous educational grant to support the opening AMD symposium. Thirteen additional companies representing a cross-section of devices and services important to vitreoretinal practice provided financial support and presented updates to the group about their businesses.

The prestigious and competitive Bausch & Lomb Retina Fellows' Forum Research award went to Arghavan Almony, MD, of the Barnes Retina Institute for her paper, "Small-Gauge Vitrectomy Does Not Protect Against Nuclear Sclerotic Cataract." Dr. Almony will present her paper at the 2010 Annual Meeting of the American Society of Retina Specialists as a specially recognized lecture.



The Fellows Forum faculty, from left, Drs. Phil Ferrone, Jeff Heier, Dean Eliott, David Chow, Steve Charles, Tarek Hassan, Carl Awh, Peter Kaiser, and Nancy Holekamp.

The meeting concluded with dinner, an informal awards ceremony, and the 5th Annual Retinal Fellows' Forum Bowling Tournament. Fellows and corporate representatives were divided into teams captained by the faculty. Phil Ferrone's team emerged victorious, aided in no small measure by his score of 220, the highest of the evening.

The 11th Annual Retina Fellows Forum will be held in Chicago on Friday, Jan. 28 through Saturday, Jan. 29, 2011.

In addition to Bausch & Lomb and Genentech, corporate support for the event was provided by Alcon, Alimera Sciences, Allergan, Carl Zeiss Meditec, Dutch Ophthalmic, Insight Instruments, Iridex, MedOne Surgical, Neovista, QLT, Quantel Medical, Synergetics and Volk Optical.

VEGF Trap Has Positive DME Data

Study Compared Drug to Laser.

■ Regeneron Pharmaceuticals and Bayer HealthCare AG reported that VEGF Trap-Eye showed positive interim results versus laser in a phase 2 study in patients with diabetic macular edema.

The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME — macular laser therapy — was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the one-year study.

"The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high levels of vascular endothelial growth factor are present," said Diana Do, MD, the principal investigator for the study and assistant professor of Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine in Baltimore.

Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared to patients receiving macular laser therapy (2.5 letters gained) at week 24. VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.

In this double-masked, prospective, randomized, multicenter phase 2 trial, entitled DA VINCI, 219 patients with clinically significant DME with central macular involvement were randomized to five groups. The control group received macular laser therapy at week one, and patients were eligible for repeat laser treatments, but no more frequently than at 16-week intervals. Two groups received monthly doses of 0.5 or 2.0 mg of VEGF Trap-Eye throughout the six-month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every eight-week dosing or as-needed dosing with specific repeat dosing criteria. Patients are continuing on the same dosing regimens for an additional 24 weeks.

Avastin Seen as Equal to Lucentis

But Genentech Takes Issue With Study.

BY JERRY HELZNER, SENIOR EDITOR

■ Researchers at Kaiser Permanante Southern California who treated 324 wet AMD patients with Avastin (bevacizumab) and 128 patients with the same disease with Lucentis (ranibizumab) found little difference between the two Genentech drugs after 12 months, both in terms of stabilizing visual acuity and in reported side effects.

Genentech was quick to point out factors that could have biased the data.

The researchers, who reported their results in the February issue of *Ophthalmology*, acknowledged the observational and nonrandomized nature of the study. However, lead author Donald Fong, MD, said that the study "should reassure patients and ophthalmologists that bevacizumab appears to be just as effective as ranibizumab."

Though the Permananente study was uncontrolled and the bevacizumab patients had an average age of 78, significantly younger than the ranibizumab patients, the researchers found that approximately one-quarter of all patients achieved close to 20/40 vision at 12 months, with little difference in adverse events.

The larger and more rigorous CATT study, which will compare Avastin and Lucentis on a head-to-head basis, is currently underway. Initial results are expected sometime in 2011.

Genentech took issue with some aspects of the Kaiser Permanente study. In a prepared statement, the company said:

"We are aware of the retrospective analysis published in the journal *Ophthalmology* titled 'Intravitreal Bevacizumab and Ranibizumab for Age-Related Macular Degeneration.' Genentech continues to believe Lucentis is the most appropriate medicine for people with wet age-related macular degeneration because it was specifically designed, formally studied, manufactured for intraocular delivery and is approved by FDA. At the same time, Genentech does not interfere with doctors' prescribing choices and believes that they should be able to prescribe the treatment they believe is most appropriate for their patients."

Genentech further asserted that "this was an uncontrolled and unmasked retrospective case analysis, with too few patients and too short a duration to adequately assess differences between the two treatment groups."

Genentech quoted Dr. Fong as stating in the article that "the sample size of the current study does not have sufficient power to determine whether there are any differences in safety." The author also notes in the conclusion of the paper, "Because the study is a nonrandomized comparison, selection bias could mask a true treatment difference."

According to Genentech, "The results beg the question as to why a higher percentage of patients switched off of Avastin than Lucentis (23% vs. 3% initially treated with Lucentis); however, the author offers only a limited explanation of this occurrence stating, 'the availability of ranibizumab most likely accounted for some of the changes observed in the bevacizumab group.'"

IN BRIEF

■ **VEGF Trap a future gold standard therapy?** In a survey of 91 US and European retina specialists, Regeneron/Bayer's as yet unapproved aflibercept (VEGF Trap-Eye) was named as a therapy for wet AMD that has the potential to reach gold-standard status. VEGF Trap-Eye is currently completing its pivotal phase 3 trials.

Decision Resources, a leading research and advisory firm for pharmaceutical and healthcare issues, reported that both Genentech's Lucentis and Regeneron/Bayer's VEGF Trap-Eye can be expected to earn Decision Resources' proprietary clinical gold standard status for wet AMD in 2013 and 2018.

A unique future gold standard cannot be identified because neither thought-leader opinion nor available clinical data can show that VEGF Trap-Eye has any advantages or disadvantages relative to Lucentis in terms of efficacy, safety and tolerability or delivery attributes.

However, Decision Resources believes that are still unmet medical needs in the treatment of wet AMD.

■ **Lux files for uveitis drug approval**. Lux Biosciences, Inc. has submitted regulatory filings to both the FDA and European Medicines Agency (EMA) seeking marketing approval for its investigational drug Luveniq (LX211) oral voclosporin for the treatment of noninfectious uveitis involving the intermediate or posterior segments of the eye.

Lux said efficacy of LX211 was demonstrated in two controlled, randomized, multicenter trials including data from 450 patients at 56 sites in seven countries. The safety data include a total of 2,110 subjects who received voclosporin during its clinical development in uveitis and psoriasis, about 500 of whom were treated for more than 36 weeks and about 200 for more than 52 weeks.

LX211 had previously received orphan drug status from the FDA and EMA, and fast-track status from the FDA. Based on the latter, Lux Biosciences has requested priority review from the FDA.

■ **Wnt pathway plays role in DR**. Scientists have identified a molecular pathway that appears to play a vital role in diabetic retinopathy. In a study appearing in the *American Journal of Pathology*, researchers show that retinal levels and nuclear translocation of beta-catenin, a key effector in the canonical Wnt pathway, were increased in humans with DR and in three DR models. Retinal levels of low-density lipoprotein receptor-related proteins 5 and 6, coreceptors of Wnts, were also elevated in the DR models.

The high glucose-induced activation of beta-catenin was attenuated by aminoguanidine, suggesting that oxidative stress is a direct cause for the Wnt pathway activation in diabetes. Indeed, Dickkopf homolog 1, a specific inhibitor of the Wnt pathway, ameliorated retinal inflammation, vascular leakage, and retinal neovascularization in the DR models. Dickkopf homolog 1 also blocked the generation of reactive oxygen species induced by high glucose, suggesting that Wnt signaling contributes to the oxidative stress in diabetes. This indicates that the Wnt pathway plays a pathogenic role in DR and represents a novel therapeutic target. **RP**

ERRATUM

In the article "Short-pulse Laser Treatment: Redefining Retinal Therapy," in the January/February 2010 issue of *Retinal Physician*, Figure 1 was mislabeled. The image is not of a rabbit eye, but of a human eye. *Retinal Physician* regrets the error.

Retinal Physician, Issue: March 2010

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Power, David
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Date
03.01.2017

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the Examining Division

on 07.06.17 at 09.00 hrs at the EPO,
PschorrHöfe, Bayerstr. 34, 80335 Munich

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC, see also OJ EPO 10/2008, 471).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, L.1., concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 04.05.17.

The actual room number as well as the waiting room numbers will be given to you by the porter in the foyer at the above EPO address.

Parking is available in the underground car park, accessible only via the entrance "Grasserstrasse 2/6". On presentation of the summons to oral proceedings at one of the porters' lodges in the PschorrHöfe, the parking ticket will be revoked.

1st Examiner:	2nd Examiner:	Chairman:
Rodrigo Simón A	Fayos C	Habedanck R

For the Examining Division

Annexes:
Confirmation of receipt (Form 2936)
Communication (EPO Form 2906)

Registered letter with advice of delivery

to EPO postal service: 22.12.16

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Application No.: 12 700 590.8

Preparation for oral proceedings - Instructions to Support Service

Oral proceedings are to be held in connection with the above patent application

1. The matters to be discussed are set out in the annex (Form 2906)

2. Dispatch the summons using Form 2008/2310 and Form 2906 for the parties to attend on:

Day 07.06.2017 Time 09:00

ROOMS

9999

Room booked

ORAL 01, 02, 03 and 05 coded

22.12.16

Date Initials

2.1 Parties' submissions in preparation for the oral proceedings, if any, should be made no later than

1 month(s)

before the date of the oral proceedings (transfer to Form 2008.1 /2310.1)

2.2 Encode ORAL(04) coded

22.12.16

Date Initials

2.3 Dispatch Form 2008.7 /2310.7 to division

22.12.16

Date Initials

3. ☐ Arrange for the following special equipment to be provided in the conference room:

Date Initials

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4. Request language service to provide simultaneous interpretation facilities as necessary

..... Date ..... Initials

5. Return the dossier to primary examiner with Form 2041 (15 days before the oral proceedings)

..... Date ..... Initials

6. Check that summons has been received (Form 2936 / advice of delivery)

7. 15 days before the oral proceedings:
- dispatch the dossier to the primary examiner.

16.12.2016
Date

Habedanck, Robert	Fayos, Cécile	Rodrigo-Simón, Ana	.....
Chairman	2nd examiner	1st examiner	Legal member

Enclosure(s):

1 The examination is being carried out on the **following application documents**

Description, Pages

1-18 as published

Sequence listings, SEQ ID NO

1, 2 as published

Claims, Numbers

1-12 filed on 17-12-2014

Drawings, Sheets

1/1 as published

2 The present application is not in accordance with the requirements of the EPC. Oral proceedings, as requested by the applicant (Art. 116 EPC), are considered expedient on the topic of Arts. 84, 54 and 56 EPC.

3 **CLARITY (Art. 84 EPC):**

Claim 11 contravenes Art. 84 EPC because the term "about" leaves the reader in doubt as to the technical features to which it refers, i.e. specific amount (i.e. mg) of VEGF antagonist to be administered.

4 The claimed compound, VEGF Trap-Eye, was also know as EYLEA, Aflibercept, VEGFR1R2-Fc[Delta]C1 (a), Zaltrap, AVE-0005, BAY-86-5321, NSC-724770, VEG Trap(R1R2) and VEGF Trap.

5 **The following prior art documents have been taken into consideration:**

D1: US2007190058

D2: US2006172944

D3: US2005163798

D4: WO0075319

D5: US2006058234

D6: US2005260203

D7: XP26732998

D8: XP009158490

D9: XP002674122

D11: XP002674124

D12: XP002674125

D13: XP002674126

D14: Hailton B Oliveira ET AL: "VEGF Trap(R1R2) suppresses experimental corneal angiogenesis", European journal of ophthalmology, 1 January 2010 (2010-01-01), page 48, XP055328439, Italy Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3709022/pdf/nihms485251.pdf

D15: ARIJIT MITRA ET AL: "Review of Anti-vascular Endothelial Growth Factor Therapy in Macular Edema Secondary to Central Retinal Vein Occlusions", EXPERT REVIEW OF OPHTHALMO, TAYLOR & FRANCIS, GB, vol. 6, no. 6, 1 January 2011 (2011-01-01), pages 623-629, XP009192770, ISSN: 1746-9899

D1 describes the treatment of (wet form) age-related macular degeneration in a mammal, comprising the steps of: a) administering to the mammal a number of first individual doses of an VEGF antagonist; and b) administering to the mammal a number of second individual doses of the VEGF antagonist, wherein the second individual doses are administered less frequently than the first individual doses (claim 1). The preferred VEGF antagonist is Ranibizumab (§112). In example 1 (Fig.1), the administration regime of the VEGF antagonist is every month (Day 0, Month 1 and 2) followed by seven doses every 3 months (P.12,§111).

D2 describes the use of VEGFR1R2-Fc [Delta]C1(a) for the treatment of eye injuries by reducing angiogenesis (§8,§17 and claims 1-2). The examples show the effect on sutured mice (i.e injury) but not on angiogenic eye disorders.

D3 describes that the fusion protein of SEQ.12 (claim 65; VEGFR1R2-Fc [Delta]C1(a)) is useful in the treatment of eye disorders as age macular degeneration and diabetic retinopathy (§122). These uses are however the selection of two lists (compounds and diseases).

D4 describes chimeric polypeptides such as VEGFR1R2-Fc [Delta]C1(a) (P.87, L.14-88) which are meant to inhibit vascular permeability for attenuation of edema among others (P. 14, L7-12).

D5 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.7-8; §67) for the treatment of age related macular degeneration and diabetic retinopathy (claim 23). These conditions are known to be improved by inhibition or reduction of VEGF, which induce undesirable plasma leakage, vascular permeability or undesirable blood vessel growth (P.2, §15).

D6 describes the use of VEGFR1R2-Fc [Delta]C1(a) (SEQ.6; claim 4) for the treatment of age related macular degeneration or diabetic retinopathy (claim 5). In D6, the examples show that VEGFR1R2-Fc [Delta]C1(a) has anti-angiogenic properties in induced ischemic retinopathy (P.7, Ex.8) and suppressed 70% of choroidal neovascularization when injected 2, 5, 8, and 11 days after laser treatment (animal model of AMD through laser disruption of Brunch's membrane) (P.8, Ex.9). Additionally, VEGFR1R2-Fc [Delta]C1(a) reduced the pathologic breakdown of the blood retinal barrier (P.8, Ex.11) and the infiltration of neutrophils and macrophages into the damaged cornea (P.9, Ex.2).

D7 (phase I; study with 21 patients), describes the improvement of best corrected visual acuity and the decrease of excess foveal thickness in patients with neovascular age-related macular degeneration patients treated with a single intravitreal injection of VEGF Trap-Eye (2-4mg).

D8 (preliminary study with 6 patients) describes that a single intravitreal injection of VEGF Trap-Eye (2mg) was well tolerated in patients with neovascular age-related macular degeneration (Abstract). The authors conclude that additional testing is to be performed by repeated injections at an interval of 6 weeks or longer (P.149, §2).

D9 describes the use of VEGF-tap-eye for the treatment of diabetic retinopathy (P.147, §4).

D11 (T-doc) reviews the known VEGF inhibitors used in ophthalmology.

D12 describes the recommended Lucentis® (Ranibizumab) dose 0.5mg to be administered by intravitreal injection once a month in the treatment of (wet) age-related macular degeneration (whole doc).

D13 (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule (whole doc).

The phase III VEGF Trap-Eye trial methodology is described in D13 but no results are provided in this document. For this reason, the cited passage of D13 cannot be considered as an enabling disclosure of the presently claimed subject-matter.

D14 describes that corneal neovascularization was known at the filing date to be treated with VEGF Trap (whole doc).

D15 describes the treatment of macular edema secondary to central retinal vein occlusion using VEGF inhibitors (whole doc).

6 **Documents and corresponding comments filed by third party observations (Art. 115 EPC) on 05.09.2016 and 07.09.2016 have been duly considered.**

OBS1: Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008

OBS2: Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008

6.1 **OBS1 and OBS2** describe the claimed dosage regime without providing any results demonstrating that it had a therapeutic effect. These documents, as already indicated for D13, cannot be considered as being enabling disclosures of the presently claimed therapeutic use.

OBS3: Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007

OBS4: WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119

OBS5: Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8

OBS6: Simo and Hernandez, Diabetes Care, Volume 32, Number 8, August 2009

OBS7: Mousa and Mousa, Biodrugs 2010; 24(3); 183-194

OBS8: Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008

6.2 **OBS3-OBS8** confirm that Aflibercerp is indeed the VEGF antagonist of the invention, i.e. compound as defined in claims 1 and 7.

Annex I: Press Release of Regeneron dated 22 November 2010

Annex II: Press Release of Regeneron dated 20 December 2010

Annex III: Article in Retinal Physician (March 2010)

6.3 **Annex I-III** are below described (point 7).

7 **NOVELTY (Art. 54 (2) EPC):**

Claims 1, 2, 4 and 7-12 are not novel in the sense of Art. 54(2) EPC in view of the following prior art:

Annex I discloses that VEGF Trap-Eye was administered every two months after three monthly loading doses (second page, third paragraph):

“In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5mg monthly, 2mg monthly, or 2mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5mg every month during the first year of the studies".

In this context, the 2 mg aflibercept dose administered in the first visit corresponds to the single initial dose of the claimed VEGF antagonist, the 2 mg aflibercept doses administered at weeks 4 and 8 correspond to two secondary doses of the claimed VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose, and the 2 mg aflibercept doses administered thereafter every 8 weeks correspond to the tertiary doses of the claimed VEGF antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline).

VEGF Trap-Eye is aflibercept ophthalmic solution (see first page, first paragraph of Annex I). Aflibercept is the same molecule as VEGFR1 R2-FcAC 1 (a) to which claim 1 refers.

According to Annex I the results of the VIEW studies show that “all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month" (cf. first page, first paragraph). This shows that a therapeutic effect is indeed obtained by treatment with a dosage regimen as required by the pending claims.

Further, Table 1 presented in Example 4 of the present application is shown on page 2 of Annex I.

7.1 **Claims 1, 2 and 7-12 are not novel in view of Annex I.**

Annex II describes a phase II study in patients with diabetic macular edema. In this study participants were randomized into one of five groups: one group receiving laser treatment (control group), two groups receiving 0.5 or 2 mg of VEGF Trap-Eye monthly, and two groups receiving three initial monthly doses of 2 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing (corresponding to the regimen defined in pending claim 1) or as-needed dosing (first page, penultimate paragraph).

Annex II reports that “the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the [DA VINCI] study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2ms dosed every other month. ” (cf, first page, penultimate paragraph)

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of Annex II.

7.2 **Claims 1, 4 and 7-12 are not novel in view of Annex II.**

Annex III discloses the dosing groups in the last paragraph of the article “VEGF Trap Has Positive diabetic macular edema Data” (on page 2/4), including two groups receiving three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline, weeks 4 and 8), followed through 24 weeks by either dosing every 8 weeks (corresponding to the regimen defined in pending claim 1) or as needed dosing. Improvements in visual acuity compared to patients receiving laser therapy were reported (§4).

7.3 **Claims 1, 4 and 7-12 are not novel in view of Annex III.**

7.4 **Claims 3, 5 and 6 are novel in the sense of Art. 54 (2) EPC because the following subject-matter has not been found to be described in the prior art at hand:** 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 two 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 4 weeks after the immediately preceding dose;wherein each tertiary dose is administered 8 weeks after the immediately preceding dose; wherein the angiogenic eye disorder is diabetic retinopathy, central retinal vein occlusion or corneal neovascularization; and wherein the VEGF antagonist comprises VEGFR1 R2-F_C ACI (a) encoded by the nucleic acid sequence of SEQ ID N0:1.

8 **INVENTIVE STEP (Art. 56 EPC):**

Claims 3, 5 and 6 are not inventive in the sense of Art. 56 EPC because:

8.1 **The closest prior art, Annex I**, describes the successful therapeutic use of the compound and dosage regime as claimed for the treatment of wet age-related macular degeneration.

8.2 **The difference** between Annex I and the present application lies in the fact that the present application proposes the use of the same compound and dosage regime for the treatment of diabetic retinopathy, central retinal vein occlusion or corneal neovascularization.

8.3 **The problem to be solved** is seen in the provision of alternative therapeutic uses of the claimed compound and dosage regime.

8.4 **In support of an inventive step** the applicant provided Exs. 1-5, directed to the treatment of age-related macular degeneration, and Ex.6 where naive patients with macular edema secondary to central retinal vein occlusion treated with 6 monthly intravitreal VEGFT injections showed reduced ocular neovascularization and improvement of visual acuity at week 24 which was maintained through week 52.

8.5 From the provided evidence, it cannot necessarily be concluded that diabetic retinopathy, central retinal vein occlusion or corneal neovascularization patients would benefit from a sequential administration of a single initial dose of a VEGF antagonist, followed by two 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 4 weeks after the immediately preceding dose; wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

A technical effect for the proposed compound and dosage regime in the treatment of diabetic retinopathy, central retinal vein occlusion or corneal neovascularization has not been demonstrated in the present application.

The problem provision of alternative therapeutic uses of the claimed compound and dosage regime has not been solved. **The objective technical problem needs to be reformulated to the less ambitious one** *"provision of a therapeutic use of the claimed dosages of a VEGF antagonist comprises VEGFR1 R2-F_C ACI (a) encoded by the nucleic acid sequence of SEQ ID N0:1",* which solution would be obvious in view of Annex I.

8.6 The same problem-solution approach would apply taking Annex II, Annex III, D1, D2, D4, D7, D8, D12 and D13 as closest prior art.

8.7 Alternatively, taking as closest prior art any of D5 or D6 or D9 (VEGF antagonist/VEGF Trap for treating diabetic retinopathy), D14 (VEGF Trap for treating corneal neovascularization) or D15 (VEGF antagonist for treating macular edema secondary to central retinal vein occlusion), the respective problems to be solved would lie in the provision of improved means to treat diabetic retinopathy, corneal neovascularization or central retinal vein occlusion.

In the present application, no experimental evidence is provided demonstrating that diabetic retinopathy, corneal neovascularization or central retinal vein occlusion are treated in an unexpected manner by the compound and dosages as claimed, compared to the VEGF antagonists and dosages of the closest prior art.

The respective problems "provision of improved means to treat the above diseases" have not been solved. They would therefore need to be reformulated to the less ambitious ones *"provision of alternative means to treat diabetic retinopathy, corneal neovascularization or central retinal vein occlusion, respectively"*, for which the claimed solution would be obvious in view of the respective closest prior art documents.

8.8 **The subject-matter of claims 3, 5 and 6 is therefore not in accordance with the requirements of Art. 56 EPC.**

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Date: 03.01.2017

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325
Applicant/Proprietor: Regeneron Pharmaceuticals, Inc.	

EPA/EPO/OEB Formblatt/Form/Formulaire : 2008

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	N400458EP

	Description of document	Original file name	Assigned file name
1	Acknowledgement	Signed acknowledgement N400458EP DXP.pdf	ADVOFDELIVRY-1.pdf

	Payment	
1	Mode of payment	Not specified

Signatures

Place:	**IONDON**
Date:	**18 January 2017**
Signed by:	**David Power 23473**
Representative name:	**David POWER**
Capacity:	**(Representative)**

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3 JANUARY 2017

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David Power (DAVID POWER)

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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	4965955	
Application number	EP12700590.8	
Date of receipt	18 January 2017	
Receiving Office	European Patent Office, The Hague	
Your reference	N400458EP	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (1 p.)	ep-sfd-request.xml ADVOFDELIVRY-1.pdf\Signed acknowledgement N400458EP DXP.pdf (1 p.)
Submitted by	CN=David Power 23473	
Method of submission	Online	
Date and time receipt generated	18 January 2017, 18:14 (CET)	
Message Digest	68:58:40:9C:B3:CF:09:E4:5C:36:41:9A:AD:D5:6F:EA:2D:2E:F5:30	

Correction by the EPO of errors in debit instructions filed by eOLF
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Bayerstrasse 34
(entrance via Zollstrasse 3)
80335 Munich
Germany

27 April 2017

FINAL SUBMISSIONS
ORAL PROCEEDINGS SCHEDULED FOR 7 JUNE 2017

Dear Sirs

European Patent Application No. 12700590.8 - 1466
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP DXP

In response to the Summons to Oral Proceedings dated 3 January 2017, I am now filing a Main Request and Auxiliary Requests 1 to 4.

For each of those Requests, please find attached a clean claim set and also a copy of the previous claims showing the amendments being made tracked-in.

Overview

Please note that the Applicant only consents to allowance based on the claims of the Main Request. If the Division, do not consider the claims of the Main Request allowable, they are asked to please then consider the claims of the Auxiliary Requests in turn and to indicate if any of the Auxiliary Requests are allowable, so that the Applicant can be consulted to see if they would be prepared to accept allowance based on that claim set.

If the Division consider that a claim set is close to allowable, but some further amendment is needed, the primary Examiner is asked to please telephone the undersigned so that the case can be discussed. I can promise a constructive approach. Further, once a claim set is agreed on, I will be happy to file a description amended for conformity with those claims.

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AMENDMENTS COMMON TO ALL CLAIM REQUESTS TO ADDRESS ITEM 4 OF THE SUMMONS

The claims sets for all of the Requests now filed have been amended to remove the word "*about*" from claim 11 rendering moot the lack of clarity objection raised in Item 3 of the Summons.

The amendments specific to each claim set are discussed further below.

MAIN REQUEST

Amendments & Basis in the claims of the Main Request

Claim 1 of the Main Request has been amended to recite that the patient is selected for treatment on the basis of not exhibiting one or more of the exclusion criteria set out in paragraph [0050] at pages 12 and 13 of the application as filed.

The claims of the Main Request also include:

- new claim 13 where the criteria set out in paragraph [0050] has been narrowed to the three specific exclusion criteria being applied; and

- new claim 14 where all of the exclusion criteria set out in paragraph [0050] are applied.

It is appreciated that the Applicant no longer has an automatic right to make voluntary amendments, but it would be greatly appreciated if additional dependent claims 13 and 14 were admitted into proceedings.

Novelty of the Main Request

None of the cited documents, including Annexes I to III on which the objections raised are based, disclose the patient being selected on the basis of not exhibiting one or more of the exclusion criteria now recited by claim 1. As such, the subject matter of the claims of the Main Request is novel over the art.

Inventive Step for the Main Request

The subject matter of the amended claims of the Main Request is also inventive over the cited art and the technical problem is solved across the full breadth of the claims.

The Summons adopts Annex I as the closest prior art. One difference between what is claimed and what is referred to in Annex I is that selection of the patient on the basis of applying at least one of the exclusion criteria set out in amended claim 1. Those exclusion criteria help ensure that the therapy is applied to the specific patient group that will particularly benefit from the therapy and for whom it is particularly appropriate. Hence:

- the **technical problem** to be solved may be formulated as the inability to start with an appropriate patient population; and

- the **solution to the technical problem** provided by the claimed approach is to identify and apply one or more of the patient exclusion criteria as set out in claim 1 of the Main Request.

The solution to that technical problem would not have been obvious from Annex I or indeed any of the cited documents.

There is no mention at all in Annex I or any of the cited prior art of exclusion criteria, Annex I therefore does not even appreciate the existence of the technical problem, still less does it disclose or suggest applying one or more of the exclusion criteria as recited by claim 1 of the Main Request. The absence of any appreciation of the technical problem would have meant that the skilled person would not even have started to consider exclusion criteria, let alone those set out in amended claim 1 of the Main Request.

There is, of course, a long line of Board of Appeal Decisions indicating that the selection of specific patient groups can represent a reason for patentability, such as T19/86, T893/90, T1399/04 and many other Board of Appeal Decisions. The amended claims of the Main Request therefore identifies a specific patient group based on their physiological or pathological status and one for which the Examples of the present application demonstrates can be treated effectively. None of the cited prior art discloses or suggests the recited patient group or even considers exclusion criteria. Without the benefit of unallowable hindsight based analysis, it is apparent that nothing in the cited art indicates to consider exclusion groups, let alone give any hint of those now recited by the claims.

The cited art lacks any mention at all of the recited criteria at all and selecting a patient group based on it. That is not just the case for Annex I, but for all of the documents cited including the alternative choices of prior art cited by the Summons. Given the absence of any indication in Annex I and any of the other cited art to even start considering exclusion criteria, let alone apply one or more of the specific exclusion criteria set out in claim 1 of the Main Request, what is claimed by the Main Request is inventive.

The Summons also questions whether the technical problem has been solved across the full scope of the claims. It is highlighted that it is reasonable to extrapolate from the specific conditions for which data is presented in the application as filed to the other conditions recited by the claims given that the conditions are inter-related and the underlying basis of the treatment is the action of the VEGF antagonist recited which is applicable to all of those conditions. There is only positive experimental data on file and no evidence has been presented to show that what is claimed would not work. The technical problem is therefore solved across the full scope of the claims.

The subject matter of the amended claims of the Main Request is therefore inventive over the cited prior art and the technical problem is solved across the full scope of the claims.

AUXILIARY REQUEST 1

The claims of Auxiliary Request 1 correspond to those of the Main Request, except that dependent claims 11 and 12 have not been included in case the Division are minded not to allow the inclusion of further dependent claims. The arguments for patentability for Auxiliary Request 1 are the same as those set out above for the claims of the Main Request.

AUXILIARY REQUEST 2

Claim 1 of Auxiliary Request 2 is focussed on one specific exclusion criteria being applied, which is any ocular or periocular infection within the last 2 weeks prior to screening. The possible exclusion criteria set out in paragraph [0050] of the application as filed has therefore been narrowed to one.

None of the cited prior art discloses or suggests the specific patient group which have not had ocular or periocular infection within the last 2 weeks prior to screening. That represents a further reason for inventive step over the art.

AUXILIARY REQUEST 3

Claim 1 of Auxiliary request 3 has been amended to narrow the exclusion criteria set out in paragraph [0050] to request that all three of the specific exclusion criteria of (1) active intraocular inflammation; (2) active ocular or periocular infection; and (3) any ocular or periocular infection within the last 2 weeks prior to treatment are applied.

The claims of Auxiliary Request 3 are therefore patentable for the additional reason that none of the cited art discloses or suggests applying all three of those specific criteria. That combination of exclusion criteria is not disclosed in any of the cited documents and that represents a further reason for inventive step over the cited art.

Given the absence of any indication in the art to even consider exclusion criteria, let alone the specific three exclusion criteria set out in claim 1 of Auxiliary Request, the skilled person would not have arrived at the claimed approach.

AUXILIARY REQUEST 4

Claim 1 of Auxiliary request 4 has been amended to narrow the exclusion criteria set out in paragraph [0050] to request that all thirty-five of the specific exclusion criteria set out in the claim are applied.

The claims of Auxiliary Request 4 are therefore patentable for the additional reason that none of the cited prior art discloses or suggests applying all thirty-five of the exclusion criteria recited. There is simply no disclosure or suggestion in any of the cited documents of all thirty-five of the recited exclusion criteria being applied. As discussed above, the cited art does not even mention exclusion criteria or provide any motivation for the skilled person to consider them, let alone those recited by the claims and even less all thirty-five of the specific exclusion criteria recited.

The claims are therefore directed to a much narrower specific patient group that cannot be in any way derived from the cited art.

CONCLUSIONS

I look forward to hearing from the Division. As indicated above, if the Division wish to discuss any points, the Examiner is welcome to telephone the undersigned.

Please note that the Applicant does not consent to amendments being made to the claims without their prior consultation, hence if the Division wish to propose amendments the Examiner is asked to please telephone the undersigned.

Yours faithfully

Electronically Signed
DR DAVID POWER
AUTHORISED REPRESENTATIVE

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	N400458EP

	Description of document	Original file name	Assigned file name
1	Amended claims (clean copy)	Main Request - clean - N400458EP DXP.PDF	CLMS-1.PDF
2	Amended claims with annotations	Main Request (tracked) N400458EP DXP.pdf	CLMS-HWA-1.pdf
3	Amended claims (clean copy)	Auxiliary Request 1 - clean - N400458EP DXP.PDF	CLMS-2.PDF
4	Amended claims with annotations	Auxiliary Request 1 (tracked) May17 N400458EP DXP.pdf	CLMS-HWA-2.pdf
5	Amended claims (clean copy)	Auxiliary Request 2 - clean - N400458EP DXP.PDF	CLMS-3.PDF
6	Amended claims with annotations	Auxiliary Request 2 - tracked - N400458EP DXP.PDF	CLMS-HWA-3.PDF
7	Amended claims (clean copy)	Auxiliary Request 3 - clean - N400458EP DXP.PDF	CLMS-4.PDF
8	Amended claims with annotations	Auxiliary Request 3 - tracked - N400458EP DXP.PDF	CLMS-HWA-4.PDF
9	Amended claims (clean copy)	Auxiliary Request 4 - clean - N400458EP DXP.PDF	CLMS-5.PDF
10	Amended claims with annotations	Auxiliary Request 4 - tracked - N400458EP DXP.PDF	CLMS-HWA-5.PDF
11	Letter relating to the search and examination procedure	Final submissions N400458EP DXP.PDF	EPLETT-1.PDF

	Payment	
1	Mode of payment	Not specified

Signatures

Place:	**London**
Date:	**27 April 2017**
Signed by:	**David Power 23473**
Representative name:	**David POWER**
Capacity:	**(Representative)**

AUXILIARY REQUEST 3

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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; wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1; and

wherein the patient is selected for treatment on the basis of not exhibiting at least the exclusion criteria (1), (2), and (3):

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

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:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

AUXILIARY REQUEST 4

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein the patient is selected for treatment on the basis of not exhibiting all of the following exclusion criteria:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

MAIN REQUEST

CLAIMS

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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; wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1; and

wherein the patient is selected for treatment on the basis of not exhibiting one or more exclusion criterion selected from the group consisting of:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to

start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

13. The pharmaceutical formulation of claim 1, wherein the exclusion criteria for the patient include at least the criteria 18, 19 and 20.

14. The formulation as claimed in claim 1, wherein the exclusion criteria for the patient include all of the criteria 1-35.

AUXILIARY REQUEST 1

CLAIMS

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1

wherein the patient is selected for treatment on the basis of not exhibiting one or more exclusion criterion selected from the group consisting of:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

AUXILIARY REQUEST 2

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein the patient is selected for treatment on the basis of not exhibiting an exclusion criterion of any ocular or periocular infection within the last 2 weeks prior to screening.

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:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

AUXILIARY REQUEST 1

CLAIMS

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1

wherein the patient is selected for treatment on the basis of not exhibiting one or more exclusion criterion selected from the group consisting of:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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 ~~about~~ 0.5 mg to ~~about~~ 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

MAIN REQUEST

CLAIMS

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1; and

wherein the patient is selected for treatment on the basis of not exhibiting one or more exclusion criterion selected from the group consisting of:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to

start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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 ~~about~~ 0.5 mg to ~~about~~ 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

13. The pharmaceutical formulation of claim 1, wherein the exclusion criteria for the patient include at least the criteria 18, 19 and 20.

14. The formulation as claimed in claim 1, wherein the exclusion criteria for the patient include all of the criteria 1-35.

AUXILIARY REQUEST 3
TRACKED

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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;

wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1; and

wherein the patient is selected for treatment on the basis of not exhibiting at least the exclusion criteria (1), (2), and (3):

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

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 ~~about~~ 0.5 mg to ~~about~~ 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

AUXILIARY REQUEST 4
TRACKED

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein the patient is selected for treatment on the basis of not exhibiting all of the following exclusion criteria:

(1) any prior ocular (in the treated 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, except dietary supplements or vitamins;

(3) prior treatment with anti-VEGF;

(4) total lesion size > 12 disc areas (30.5 mm2, including blood, scars and neovascularization) as assessed by FA;

(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 treated eye;

(6) scar or fibrosis, making up > 50% of total lesion in the treated 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 treated eye;

(9) history of any vitreous hemorrhage within 4 weeks prior to treatment;

(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 treated 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;

(13) history of retinal detachment or treatment or surgery for retinal detachment;

(14) history of macular hole of stage 2 and above;

(15) any intraocular or periocular surgery within 3 months of start of treatment, except lid surgery, which may not have taken place within 1 month of start of treatment, as long as it is unlikely to interfere with injection;

(16) prior trabeculectomy or other filtration surgery;

(17) uncontrolled glaucoma (defined as intraocular pressure greater than or equal to 25 mm Hg despite treatment with anti-glaucoma medication);

(18) active intraocular inflammation;

(19) active ocular or periocular infection;

(20) any ocular or periocular infection within the last 2 weeks prior to treatment;

(21) history of uveitis;

(22) active scleritis or episcleritis;

(23) presence or history of scleromalacia;

(24) aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy);

(25) previous therapeutic radiation in the region;

(26) history of corneal transplant or corneal dystrophy;

(27) significant media opacities, including cataract, which might interfere with visual acuity, assessment of safety, or fundus photography;

(28) any concurrent intraocular condition (e.g. cataract) that could require either medical or surgical intervention during the treatment period;

(29) any concurrent ocular condition which 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 render the subject at high risk for treatment complications;

(31) systemic or ocular treatment with an investigational agent in the past 3 months prior to start of treatment;

(32) use of long acting steroids, either systemically or intraocularly, in the 6 months prior to start of treatment;

(33) history of allergy to povidone iodine;

(34) known serious allergy to the fluorescein sodium for injection in angiography; and

(35) presence of any contraindications indicated in the FDA approved label for ranibizumab (Lucentis®).

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 ~~about~~ 0.5 mg to ~~about~~ 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

AUXILIARY REQUEST 2
TRACKED

1. 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 two 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 4 weeks after the immediately preceding dose;

wherein each tertiary dose is administered 8 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 VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein the patient is selected for treatment on the basis of not exhibiting an exclusion criterion of any ocular or periocular infection within the last 2 weeks prior to screening.

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 ~~about~~ 0.5 mg to ~~about~~ 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein:

(a) all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist; or

(b) all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

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Application number	EP12700590.8
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Documents submitted

package-data.xml	ep-sfd-request.xml
epf1038.pdf (2 p.)	CLMS-1.PDF\Main Request - clean - N400458EP DXP.PDF (4 p.)
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* Zulassung ruht

Filed via epoline
Europäisches Patentamt

80298 München

URGENT!
Please forward to the Examining Division immediately!

Munich, 15 May 2016

Application No.: EP 12 700 590.8
Applicant: Regeneron Pharmaceuticals, Inc.

Our ref.: 9281-TPO / RN

Observations pursuant to Article 115 EPC regarding European patent application 12 700 590.8

In accordance with Article 115 EPC, Third Party Observations against European patent application EP 12 700 590.8 (EP 2 663 325 A1) are filed on behalf of

bioeq GmbH
Tölzer Straße 12
83607 Holzkirchen
Germany

For the reasons set forth below, the requests filed with applicant's submission of 27 April 2017 are **not in compliance with the requirements of the EPC**.

RN:LA

Reference is made to the previous Third Party Observations filed on 7 September 2016.

1. Inadmissible extension (Article 123(2) EPC)

1.1 Main Request and Auxiliary Request 1

a) Claim 1 of the Main Request and Auxiliary Request 1 has been amended to require that the patient which is selected for treatment does not exhibit one or more of the exclusion criteria (1) to (35) listed in the claim. is applied to select the patient for treatment.

However, paragraph [0050] of the application does not directly and unambiguously disclose that only one or some exclusion criteria is to be applied. Rather, it is apparent form the overall context of the example that all exclusion criteria listed in this paragraph should be applied when selecting the patient for treatment.

In addition, it is apparent that the exclusion criteria of paragraph [0050] are not correctly reproduced in claim 1 of the Main Request and Auxiliary Request 1.

b) For example, criterion (3) of claim 1 simply refers to "prior treatment with anti-VEGF", indicating that any prior treatment with an anti-VEGF agent is excluded. However, exclusion criterion (3) of paragraph [0050] does not generally exclude treatment of patients who have been subjected to anti-VEGF therapy before, but defines three subcriteria which lead to an exclusion of the patient (prior treatment in the study eye, prior treatment in the fellow eye with an investigational agent less than 3 months prior to a first dose, prior systemic anti-VEGF therapy less than 3 months prior to first

dose). Accordingly, criterion (3) of claim 1 does not find a basis in the application as filed.

c) Further, several criteria of paragraph [0050] of the application differentiate between conditions in the study eye and conditions in both the study eye and the fellow eye ("in either eye"). In contrast, the corresponding criteria in claim 1 do not specify in which eye the condition should not occur for the patient to receive the treatment. This applies to criteria (4), (9), (12), (13), (14), (15), (16), (17), (24), (25), (26), (27) and (28) of claim 1 which according to paragraph [0050] of the application only apply to the study eye, whereas the corresponding criteria of claim 1 do not contain this limitation.

d) The criteria introduced into claim 1 are only disclosed in the context of a specific example in which VEGF-trap was administered to patients with age-related macular degeneration by intravitreal injection (see title of example 4). The only patient group which received a treatment with an intial dose, secondary and tertiary doses as required by the claim received 2 mg VEGF-trap every four weeks to week 8, i.e. an initial dose at week 0 and two secondary doses at weeks 4 and 8, and then tertiary doses of 2 mg every eight weeks until week 96 (see paragraph [0043] of the application).

Accordingly, the application as filed does not provide a basis for the following features in the context of the exclusion criteria listed in claim 1:

- more than two secondary doses of the VEGF antagonist (claim 1);
- an indefinite number of tertiary doses of the VEGF antagonist (claim 1);

- the treatment of diabetic retinopathy, diabetic macular edema[1], central retinal vein occlusion and corneal neovascularization (claims 1 and 3-6);
- the administration of the VEGF antagonist by topical or intraocular administration (claims 8 and 9);
- the administration of doses of the VEGF antagonist other than 2 mg such as 0.5 mg (claims 11 and 12).

In summary, the Main Request and Auxiliary Request 1 do not meet the requirements of Article 123(2) EPC.

1.2 Auxiliary Request 2

According to Auxiliary Request 2 only one exclusion criterion is to be applied, i.e. any ocular or periocular infection within the last two weeks prior to screening.

To this request at least argument d) discussed with respect to the Main Request and Auxiliary Request 1 applies in that some features of the claims of this request are not disclosed in the context of the specific example from which the list of exclusion criteria was taken.

1.3 Auxiliary Request 3

Claim 1 of Auxiliary Request 3 requires that all three specific exclusion criteria listed in said claim are applied.

[1] Reference is made to exclusion criterion (11) which explicitly excludes patients with diabetic retinopathy and diabetic macular edema from therapy.

Paragraph [0050] of the application lists 37 criteria without indicating that some of these criteria are more relevant than others for the treatment of the patients. Hence, the selection of the three criteria present in claim 1 of Auxiliary Request 3 is not directly and unambiguously derivable from the application as filed. According to established case law the multiple selection of elements from one list of considerable length is equivalent to a selection of elements from two lists (see T 1374/07, T 2375/09 and T 1506/13) and contravenes Article 123(2) EPC.

Additionally argument d) as discussed above with respect to the Main Request and Auxiliary Request 1 also applies to this request.

1.4 Auxiliary Request 4

According to claim 1 of Auxiliary Request 4 all 35 exclusion criteria are applied.

To this request arguments b), c) and d) as discussed above for the Main Request and Auxiliary Request 1 apply.

2. Lack of inventive step (Article 56 EPC)

2.1 Main Request and Auxiliary Request 1

The applicant argues that *"the exclusion criteria help ensure that the therapy is applied to the specific patient group that will particularly benefit from the therapy and for whom it is particularly appropriate."* Further it submits that Annex 1 is silent on any exclusion criteria so that the skilled person would not have considered these criteria. Based on these considerations the subject-matter of the requests is said to be inventive.

However, the fact that Annex 1 does not mention any exclusion criteria does not mean that such criteria were not applied in the clinical study the results of which are reported in Annex 1. Herewith a description of the VIEW2 clinical study in clinicaltrials.gov of 30 November 2010, i.e. before the priority date of the present application, is filed as Annex 4. It is apparent from this document that several exclusion criteria were applied to select the patients to be treated. These exclusion criteria are nearly identical to those listed in the Main Request and Auxiliary Request 1. Hence, in the very same study the results of which are reported in Annex 1 essentially the same exclusion criteria were applied, meaning that the skilled person indeed not only considered some exclusion criteria for patient selection, but the same exclusion criteria as those used in the present application.

Additionally, in Example 4 of the application the patient group to be treated is not only defined by the exclusion criteria (1) to (37), but also by inclusion criteria (i) to (vii) (see paragraph [0049] of the application). In particular, to be eligible for the study subjects were required to have subfoveal choroidal neovascularization secondary to AMD (see paragraph [0047] and inclusion criterion (iii) of paragraph [0049] of the application). It may be assumed that for the treatment success the selection of patients meeting this inclusion criterion is at least as important as the selection of patients not meeting the exclusion criteria. Hence, also for this reason the selection of patients as defined in claim 1 does not involve an inventive step.

2.2 Auxiliary Requests 2 and 3

The exclusion criteria listed in claim 1 of Auxiliary Requests 2 and 3 are not mentioned in Annex 4. However, the application does not provide any data from which it can be derived that these criteria are more important than the

other 34 or 36 criteria, respectively, listed in paragraph [0050] of the application, i.e. that the selection of these criteria has any effect on the treatment success. Annex 4 shows that the skilled person indeed considered exclusion criteria for a treatment of AMD with VEGF-trap.

Additionally, the arguments with respect to the inclusion criteria mentioned in paragraph 2.1 also apply to Auxiliary Requests 2 and 3.

3. Lack of clarity (Article 84 EPC)

As briefly mentioned above, claim 1 of the Main Request, Auxiliary Request 1 and Auxiliary Request 4 comprises the treatment of, inter alia, diabetic retinopathy and diabetic macular edema. However, criterion (11) excludes patients with history or clinical evidence of diabetic retinopathy and diabetic macular edema. It is not clear how patients with these diseases can be treated, if according to criterion (11) patients with these diseases are to be excluded.

4. Conclusion

The subject-matter of all requests on file does not meet the requirements of Article 123(2) EPC. Additionally, the selection of exclusion criteria does not involve an inventive step. Finally, the claims of the Main Request, Auxiliary Request 1 and Auxiliary Request 4 do not meet the requirements of Article 84 EPC.

Thus, all requests on file do not meet the requirements of the EPC.

Andrea Lasar

Maiwald Patentanwalts GmbH
(Andrea Lasar)

Encls.
Annex 4

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	9281-TPO/RN

	Description of document	Original file name	Assigned file name
1	Citations filed by a third party	9281-TPO_Annex 4.PDF	TDOC-1.PDF
2	Observations by third parties (Art. 115 EPC)	9281-TPO_TPO.pdf	TIPA1-1.pdf

	Payment	
1	Mode of payment	Not specified

Signatures

Place:	**Munich**
Date:	**15 May 2017**
Signed by:	**Andrea Lasar 13617**
Representative name:	**Andrea LASAR**
Capacity:	**(Representative)**

Annex 4

View of NCT00637377 on 2010_11_30

ClinicalTrials Identifier: NCT00637377
Updated: 2010_11_30

Descriptive Information

Brief title
Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)

Official title
A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)

Brief summary

This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Active Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (ie, prevention of moderate vision loss) Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52 Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: The proportion of subjects who gain at least 15 letters of vision at Week 52 Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in total NEI VFQ-25 score at Week 52

	Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in CNV area at Week 52 Time Frame: week 52 Safety Issue? Yes
Enrollment	1240 (Actual)
Condition	Macular Degeneration
Arm/Group	Arm Label: Arm 3 Experimental
Arm/Group	Arm Label: Arm 1 Experimental
Arm/Group	Arm Label: Arm 2 Experimental
Arm/Group	Arm Label: Arm 4 Active Comparator
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 1 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 2 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 3 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: Ranibizumab Arm Label: Arm 4 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
URL	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
URL	http://www.fda.gov/medwatch/safety.htm
URL	http://www.clinicalstudyresults.org
See also	Click here and search for drug information provided by the FDA.
See also	Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product.
See also	Click here to find results for studies related to marketed products.

Recruitment Information

Status	Active, not recruiting
Start date	2008-04
Last follow-up date	2011-08 (Anticipated)
Primary completion date	2010-09 (Actual)

Criteria

Inclusion Criteria:
-Signed informed consent.
-Men and women >/=50 years of age.
-Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
-ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study
eye at 4 meters.
-Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
-Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria:
-Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.
-Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
-Any prior treatment with anti-VEGF agents in the study eye.
-Total lesion size >12 disc areas (30.5 mm, including blood, scars and neovascularization) as assessed by FA in the study eye.
-Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
-Scar or fibrosis making up >50% of the total lesion in the study eye.
-Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
-History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
-Presence of other causes of CNV in the study eye.
-Prior vitrectomy in the study eye.
-History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
-Any history of macular hole of stage 2 and above in the study eye.
-Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
-History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Gender	Both
Minimum age	50 Years
Healthy volunteers	No

Administrative Data

Organization name	Bayer
Organization study ID	91689
Secondary ID	EurdaCT No.: 2007-000583-25
Sponsor	Bayer
Health Authority	Switzerland: Swiss Medic
Health Authority	Argentina: Ministry of Health
Health Authority	Australia: Department of Health and Ageing Therapeutic Goods

	Administration
Health Authority	Austria: Federal Office for Safety in Health Care
Health Authority	Belgium: Federal Agency for Medicinal Products and Health Products
Health Authority	Brazil: ANVISA Agencia Nacional de Vigilancia Sanitaria
Health Authority	Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
Health Authority	Czech Republic: State Institute for Drug Control
Health Authority	France: Afssaps - French Health Products Safety Agency
Health Authority	Germany: Federal Institute for Drugs and Medical Devices
Health Authority	Hungary: National Institute of Pharmacy
Health Authority	India: Drugs Controller General of India
Health Authority	Israel: Ministry of Health
Health Authority	Italy: Ethics Committee
Health Authority	Japan: Pharmaceuticals and Medical Devices Agency
Health Authority	South Korea: Korea Food and Drug Administration (KFDA)
Health Authority	Latvia: State Agency of Medicines
Health Authority	Mexico: Federal Commission for Sanitary Risks Protection
Health Authority	Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Health Authority	Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Health Authority	Portugal: INFARMED National Authority of Medicines and Health Products
Health Authority	Singapore: Health Sciences Authority
Health Authority	Slovakia: State Institute for Drug Control
Health Authority	Spain: Ministry of Health and Consumption
Health Authority	Sweden: Medical Products Agency
Health Authority	United Kingdom: Medicines and Healthcare Products Regulatory Agency

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	5279258
Application number	EP12700590.8
Date of receipt	15 May 2017
Receiving Office	European Patent Office, The Hague
Your reference	9281-TPO/RN
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (1 p.) TIPA1-1.pdf\9281-TPO_TPO.pdf (7 p.) ep-sfd-request.xml TDOC-1.PDF\9281-TPO_Annex 4.PDF (4 p.)
Submitted by	CN=Andrea Lasar 13617
Method of submission	Online
Date and time receipt generated	15 May 2017, 13:58 (CEST)
Message Digest	58:03:08:48:F1:51:4A:C9:02:AD:06:CD:46:3C:17:61:1B:DF:23:3E

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

********** -KOMM.BERICHT- ********** DATUM 23-MAI-2017 ** UHRZEIT 13:48 ********

MODUS = SPEICHER-ÜBERTRAGUNG START=23-MAI 13:46 ENDE=23-MAI 13:48

DATEI-NR.=225

STN NR.	KOMM.	ZIELWAHL / KURZWAHL	NAME/ E-MAIL-ADRESSE/ RUFNUMMER	SEITEN	DAUER
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-EUROPEAN PATENT OFFICE -

***** UF-8300 ********** -MUNICH N143 001 - ***** - 0049 89 23994465- *********

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Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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23.05.17
Prior by Fax: +44 207430 1000

Date: 31.05.2017

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325

Applicant/Proprietor: Regeneron Pharmaceuticals, Inc.

BRIEF COMMUNICATION

Oral Proceedings on 07.06.17 at 09:00 hours

Subject:
- [x] Your letter of 27.04.2017
- [ ] Cancellation / postponement at the instigation of the division

Communication:

1. [x] The date / time fixed for oral proceedings is maintained.
   - [ ] The reasons are indicated on enclosed EPO Form 2906.
2. [ ] The request for the oral proceedings to be held as a videoconference is rejected. The reasons are indicated on enclosed EPO Form 2906.
3. [ ] The above-mentioned oral proceedings will start at ..... hours.
4. [ ] The summons to attend oral proceedings on the above-mentioned date is cancelled.
   - 4.1
     - [ ] The reasons are indicated on enclosed EPO Form 2906.
     - [ ] The procedure will be continued in writing.
     - [ ] A new date will be set later.
     - [ ] New summons will follow.
   - 4.2 [ ] Due to administrative reasons the oral proceedings have to be postponed to a later date. New summons will follow.
   - 4.3 [ ] The application is deemed to be withdrawn. The right to oral proceedings only persists as long as proceedings are pending.

Please take note.

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
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Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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Date
24.05.2017

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325
Applicant/Proprietor	
Regeneron Pharmaceuticals, Inc.	

Communication pursuant to Rule 114(2) EPC

Please find enclosed observations by a third party concerning the patentability of the invention of the above-mentioned patent application. That person is not a party to the proceedings before the EPO (Art. 115 EPC).

Under Rule 114(2) EPC you may comment on the observations.

For the Examining Division

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Amtsgericht München

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GF (Geschäftsführer), C (Counsel), PA (Patentanwalt), EPA (European Patent Attorney), FA (Fachanwalt für gewerblichen Rechtsschutz)
MUC (München), DUS (Düsseldorf)
* Zulassung ruht

Filed via epoline
Europäisches Patentamt

80298 München

URGENT!
Please forward to the Examining Division immediately!

Munich, 15 May 2016

Application No.: EP 12 700 590.8
Applicant: Regeneron Pharmaceuticals, Inc.

Our ref.: 9281-TPO / RN

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bioeq GmbH
Tölzer Straße 12
83607 Holzkirchen
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RN:LA

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dose). Accordingly, criterion (3) of claim 1 does not find a basis in the application as filed.

c) Further, several criteria of paragraph [0050] of the application differentiate between conditions in the study eye and conditions in both the study eye and the fellow eye ("in either eye"). In contrast, the corresponding criteria in claim 1 do not specify in which eye the condition should not occur for the patient to receive the treatment. This applies to criteria (4), (9), (12), (13), (14), (15), (16), (17), (24), (25), (26), (27) and (28) of claim 1 which according to paragraph [0050] of the application only apply to the study eye, whereas the corresponding criteria of claim 1 do not contain this limitation.

d) The criteria introduced into claim 1 are only disclosed in the context of a specific example in which VEGF-trap was administered to patients with age-related macular degeneration by intravitreal injection (see title of example 4). The only patient group which received a treatment with an intial dose, secondary and tertiary doses as required by the claim received 2 mg VEGF-trap every four weeks to week 8, i.e. an initial dose at week 0 and two secondary doses at weeks 4 and 8, and then tertiary doses of 2 mg every eight weeks until week 96 (see paragraph [0043] of the application).

Accordingly, the application as filed does not provide a basis for the following features in the context of the exclusion criteria listed in claim 1:

- more than two secondary doses of the VEGF antagonist (claim 1);
- an indefinite number of tertiary doses of the VEGF antagonist (claim 1);

- the treatment of diabetic retinopathy, diabetic macular edema[1], central retinal vein occlusion and corneal neovascularization (claims 1 and 3-6);
- the administration of the VEGF antagonist by topical or intraocular administration (claims 8 and 9);
- the administration of doses of the VEGF antagonist other than 2 mg such as 0.5 mg (claims 11 and 12).

In summary, the Main Request and Auxiliary Request 1 do not meet the requirements of Article 123(2) EPC.

1.2 Auxiliary Request 2

According to Auxiliary Request 2 only one exclusion criterion is to be applied, i.e. any ocular or periocular infection within the last two weeks prior to screening.

To this request at least argument d) discussed with respect to the Main Request and Auxiliary Request 1 applies in that some features of the claims of this request are not disclosed in the context of the specific example from which the list of exclusion criteria was taken.

1.3 Auxiliary Request 3

Claim 1 of Auxiliary Request 3 requires that all three specific exclusion criteria listed in said claim are applied.

[1] Reference is made to exclusion criterion (11) which explicitly excludes patients with diabetic retinopathy and diabetic macular edema from therapy.

Paragraph [0050] of the application lists 37 criteria without indicating that some of these criteria are more relevant than others for the treatment of the patients. Hence, the selection of the three criteria present in claim 1 of Auxiliary Request 3 is not directly and unambiguously derivable from the application as filed. According to established case law the multiple selection of elements from one list of considerable length is equivalent to a selection of elements from two lists (see T 1374/07, T 2375/09 and T 1506/13) and contravenes Article 123(2) EPC.

Additionally argument d) as discussed above with respect to the Main Request and Auxiliary Request 1 also applies to this request.

1.4 Auxiliary Request 4

According to claim 1 of Auxiliary Request 4 all 35 exclusion criteria are applied.

To this request arguments b), c) and d) as discussed above for the Main Request and Auxiliary Request 1 apply.

2. Lack of inventive step (Article 56 EPC)

2.1 Main Request and Auxiliary Request 1

The applicant argues that *"the exclusion criteria help ensure that the therapy is applied to the specific patient group that will particularly benefit from the therapy and for whom it is particularly appropriate."* Further it submits that Annex 1 is silent on any exclusion criteria so that the skilled person would not have considered these criteria. Based on these considerations the subject-matter of the requests is said to be inventive.

However, the fact that Annex 1 does not mention any exclusion criteria does not mean that such criteria were not applied in the clinical study the results of which are reported in Annex 1. Herewith a description of the VIEW2 clinical study in clinicaltrials.gov of 30 November 2010, i.e. before the priority date of the present application, is filed as Annex 4. It is apparent from this document that several exclusion criteria were applied to select the patients to be treated. These exclusion criteria are nearly identical to those listed in the Main Request and Auxiliary Request 1. Hence, in the very same study the results of which are reported in Annex 1 essentially the same exclusion criteria were applied, meaning that the skilled person indeed not only considered some exclusion criteria for patient selection, but the same exclusion criteria as those used in the present application.

Additionally, in Example 4 of the application the patient group to be treated is not only defined by the exclusion criteria (1) to (37), but also by inclusion criteria (i) to (vii) (see paragraph [0049] of the application). In particular, to be eligible for the study subjects were required to have subfoveal choroidal neovascularization secondary to AMD (see paragraph [0047] and inclusion criterion (iii) of paragraph [0049] of the application). It may be assumed that for the treatment success the selection of patients meeting this inclusion criterion is at least as important as the selection of patients not meeting the exclusion criteria. Hence, also for this reason the selection of patients as defined in claim 1 does not involve an inventive step.

2.2 Auxiliary Requests 2 and 3

The exclusion criteria listed in claim 1 of Auxiliary Requests 2 and 3 are not mentioned in Annex 4. However, the application does not provide any data from which it can be derived that these criteria are more important than the

other 34 or 36 criteria, respectively, listed in paragraph [0050] of the application, i.e. that the selection of these criteria has any effect on the treatment success. Annex 4 shows that the skilled person indeed considered exclusion criteria for a treatment of AMD with VEGF-trap.

Additionally, the arguments with respect to the inclusion criteria mentioned in paragraph 2.1 also apply to Auxiliary Requests 2 and 3.

3. Lack of clarity (Article 84 EPC)

As briefly mentioned above, claim 1 of the Main Request, Auxiliary Request 1 and Auxiliary Request 4 comprises the treatment of, inter alia, diabetic retinopathy and diabetic macular edema. However, criterion (11) excludes patients with history or clinical evidence of diabetic retinopathy and diabetic macular edema. It is not clear how patients with these diseases can be treated, if according to criterion (11) patients with these diseases are to be excluded.

4. Conclusion

The subject-matter of all requests on file does not meet the requirements of Article 123(2) EPC. Additionally, the selection of exclusion criteria does not involve an inventive step. Finally, the claims of the Main Request, Auxiliary Request 1 and Auxiliary Request 4 do not meet the requirements of Article 84 EPC.

Thus, all requests on file do not meet the requirements of the EPC.

Andrea Lasar

Maiwald Patentanwalts GmbH
(Andrea Lasar)

Encls.
Annex 4

Annex 4

← History of this study ↑ Current version of this study

View of NCT00637377 on 2010_11_30

ClinicalTrials Identifier: NCT00637377
Updated: 2010_11_30

Descriptive Information

Brief title Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)

Official title A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)

Brief summary

This study is a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America.

Detailed description

Phase	Phase 3
Study type	Interventional
Study design	Treatment
Study design	Randomized
Study design	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Study design	Active Control
Study design	Parallel Assignment
Study design	Safety/Efficacy Study
Primary outcome	Measure: The proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (ie, prevention of moderate vision loss) Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52 Time Frame: week 52 Safety Issue? Yes
Secondary outcome	Measure: The proportion of subjects who gain at least 15 letters of vision at Week 52 Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in total NEI VFQ-25 score at Week 52

	Time Frame: week 52 Safety Issue? No
Secondary outcome	Measure: Mean change from baseline in CNV area at Week 52 Time Frame: week 52 Safety Issue? Yes
Enrollment	1240 (Actual)
Condition	Macular Degeneration
Arm/Group	Arm Label: Arm 3 Experimental
Arm/Group	Arm Label: Arm 1 Experimental
Arm/Group	Arm Label: Arm 2 Experimental
Arm/Group	Arm Label: Arm 4 Active Comparator
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 1 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 2 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: VEGF Trap-Eye (BAY86-5321) Arm Label: Arm 3 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
Intervention	Drug: Ranibizumab Arm Label: Arm 4 0.5 mg administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
URL	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
URL	http://www.fda.gov/medwatch/safety.htm
URL	http://www.clinicalstudyresults.org
See also	Click here and search for drug information provided by the FDA.
See also	Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product.
See also	Click here to find results for studies related to marketed products.

Recruitment Information

Status	Active, not recruiting
Start date	2008-04
Last follow-up date	2011-08 (Anticipated)
Primary completion date	2010-09 (Actual)

Criteria

Inclusion Criteria:
-Signed informed consent.
-Men and women >/=50 years of age.
-Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye.
-ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study
eye at 4 meters.
-Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
-Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.

Exclusion Criteria:
-Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements or vitamins.
-Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye.
-Any prior treatment with anti-VEGF agents in the study eye.
-Total lesion size >12 disc areas (30.5 mm, including blood, scars and neovascularization) as assessed by FA in the study eye.
-Subretinal hemorrhages that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye (if the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
-Scar or fibrosis making up >50% of the total lesion in the study eye.
-Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
-History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
-Presence of other causes of CNV in the study eye.
-Prior vitrectomy in the study eye.
-History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
-Any history of macular hole of stage 2 and above in the study eye.
-Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection.
-History or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye.

Gender	Both
Minimum age	50 Years
Healthy volunteers	No

Administrative Data

Organization name	Bayer
Organization study ID	91689
Secondary ID	EurdaCT No.: 2007-000583-25
Sponsor	Bayer
Health Authority	Switzerland: Swiss Medic
Health Authority	Argentina: Ministry of Health
Health Authority	Australia: Department of Health and Ageing Therapeutic Goods

	Administration
Health Authority	Austria: Federal Office for Safety in Health Care
Health Authority	Belgium: Federal Agency for Medicinal Products and Health Products
Health Authority	Brazil: ANVISA Agencia Nacional de Vigilancia Sanitaria
Health Authority	Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
Health Authority	Czech Republic: State Institute for Drug Control
Health Authority	France: Afssaps - French Health Products Safety Agency
Health Authority	Germany: Federal Institute for Drugs and Medical Devices
Health Authority	Hungary: National Institute of Pharmacy
Health Authority	India: Drugs Controller General of India
Health Authority	Israel: Ministry of Health
Health Authority	Italy: Ethics Committee
Health Authority	Japan: Pharmaceuticals and Medical Devices Agency
Health Authority	South Korea: Korea Food and Drug Administration (KFDA)
Health Authority	Latvia: State Agency of Medicines
Health Authority	Mexico: Federal Commission for Sanitary Risks Protection
Health Authority	Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
Health Authority	Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Health Authority	Portugal: INFARMED National Authority of Medicines and Health Products
Health Authority	Singapore: Health Sciences Authority
Health Authority	Slovakia: State Institute for Drug Control
Health Authority	Spain: Ministry of Health and Consumption
Health Authority	Sweden: Medical Products Agency
Health Authority	United Kingdom: Medicines and Healthcare Products Regulatory Agency

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Questions about this communication ?
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Maiwald
Patentanwaltsgesellschaft mbH
Elisenstrasse 3
80335 München

Date: 24.05.2017

Reference	Application No./Patent No.
9281-TPO / RN	12700590.8 - 1466 / 2663325

Applicant/Proprietor: Regeneron Pharmaceuticals, Inc.

Acknowledgment of receipt of observations by third parties (Article 115 EPC)

Receipt of your letter dated 15.05.2017 is hereby acknowledged.

Under Article 115 EPC you will not be a party to the proceedings before the European Patent Office.

☐ In your letter the following documents are mentioned which were not enclosed, and which are not available in the EPO:

☐ The third party observations have not been filed in an official language of the EPO (R. 114(1) EPC).

You are requested to file copy(ies) and/or translation(s) in one of the official EPO languages within **two months** of notification of this communication if they are to be taken into account.

For the Examining Division

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GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Power, David
J A Kemp
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ROYAUME UNI

Date: 31.05.2017

Reference	Application No./Patent No.
N400458-EP DXP	12700590.8 - 1466 / 2663325

Applicant/Proprietor: Regeneron Pharmaceuticals, Inc.

BRIEF COMMUNICATION

Oral Proceedings on 07.06.17 at 09:00 hours

Subject:
- [X] Your letter of 27.04.2017
- [ ] Cancellation / postponement at the instigation of the division

Communication:

1. [X] The date / time fixed for oral proceedings is maintained.
   - [ ] The reasons are indicated on enclosed EPO Form 2906.
2. [ ] The request for the oral proceedings to be held as a videoconference is rejected. The reasons are indicated on enclosed EPO Form 2906.
3. [ ] The above-mentioned oral proceedings will start at ..... hours.
4. [ ] The summons to attend oral proceedings on the above-mentioned date is cancelled.

4.1
- [ ] The reasons are indicated on enclosed EPO Form 2906.
- [ ] The procedure will be continued in writing.
- [ ] A new date will be set later.
- [ ] New summons will follow.

4.2 [ ] Due to administrative reasons the oral proceedings have to be postponed to a later date. New summons will follow.

4.3 [ ] The application is deemed to be withdrawn. The right to oral proceedings only persists as long as proceedings are pending.

Please take note.

Registered letter
EPO Form 2008A 03.16 (23/05/17)

CK23171

For the Examining Division

☐ Enclosure : EPO Form 2906

J A • K E M P

BY ONLINE FILING

The European Patent Office
Bayerstrasse 34
(entrance via Zollstrasse 3)
80335 Munich
Germany

URGENT ORAL PROCEEDINGS SCHEDULED FOR 7 JUNE 2017

5 June 2017

Dear Sirs

European Patent Application No. 12700590.8 - 1466
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP DXP/nxo

I withdraw my previous request for Oral Proceedings on the present application. I also withdraw the present application itself.

Yours faithfully

Electronically Signed
DR DAVID POWER
AUTHORISED REPRESENTATIVE

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
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Office européen des brevets

Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	12700590.8
Applicant's or representative's reference	N400458EP

	Description of document	Original file name	Assigned file name
1	Withdrawal of an application	withdraw N400458EP DXP.pdf	WDRA-1.pdf

	Payment	
1	Mode of payment	Not specified

Signatures

Place:	**London**
Date:	**05 June 2017**
Signed by:	**David Power 23473**
Representative name:	**David POWER**
Capacity:	**(Representative)**

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European Patent Office
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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	5336000	
Application number	EP12700590.8	
Date of receipt	05 June 2017	
Receiving Office	European Patent Office, The Hague	
Your reference	N400458EP	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (1 p.)	ep-sfd-request.xml WDRA-1.pdf\withdraw N400458EP DXP.pdf (1 p.)
Submitted by	CN=David Power 23473	
Method of submission	Online	
Date and time receipt generated	05 June 2017, 12:50 (CEST)	
Message Digest	A2:41:34:84:6F:0F:03:8A:EC:5F:88:62:C0:A9:F6:1F:FD:88:1F:9B	

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Closure of the procedure in respect of application No. 12700590.8 - 1466 06.06.17

1. **The procedure in respect of the above application is closed for the following reason:**

   X WDRA 05.06.17 The application has been withdrawn.

2. **The EPASYS situation has been verified in respect of item 1:**

   DFIL: 11.01.12

   NOAP: ////

   RDEC: ////

   RFPR: //

   REES: ///

   REFU 3/ADWI 3 and DEAD 1 coded. Date of legal effect 05.06.2017

3. **Position regarding fees:**

DEST03	005	00858981	05.07.13	EUR	555,00
EXAM02	006	00858981	05.07.13	EUR	1 730,00
FFEE01	020	00858981	05.07.13	EUR	115,00
RFEE 03	033	00547566	27.01.14	EUR	445,00
RFEE 04	034	00553999	27.01.15	EUR	580,00
RFEE 05	035	00564053	28.01.16	EUR	810,00
RFEE 06	036	00551546	24.01.17	EUR	1 050,00

   ☐ Examination started on _____ (EXDS51).

   ☐ Refund(s) ordered:

   ☐ 100% EXAM fee** ☐ 75% EXAM fee** ☐ 50% EXAM fee**

   ☐ DEST fee* ☐ RFEE(s): _____ ☐ Other fees: _____

   Note: Attention is to be paid to potential automated refund proposal(s).

   * Refund of DEST fee if date of legal effect is before/on SEPU or PACT6 date.

   * * PLEASE REVIEW REFUND OF EXAMINATION FEE (100% or 75% or 50%)

4. **Mark "DEAD" on the paper file and:**

   ☒ Check whether a divisional application is pending and if so attach the DEAD file to it.

   ☐ Any **models** still in the Office's possession were returned on _____ (for dealing with models, please refer to Fil d'Ariane).

   ☐ Keep paper file in file store (separate place) until next action for file destruction.

06.06.2017 Christensen, Jette

Date Formalities Officer

EPO Form 2058 11.16