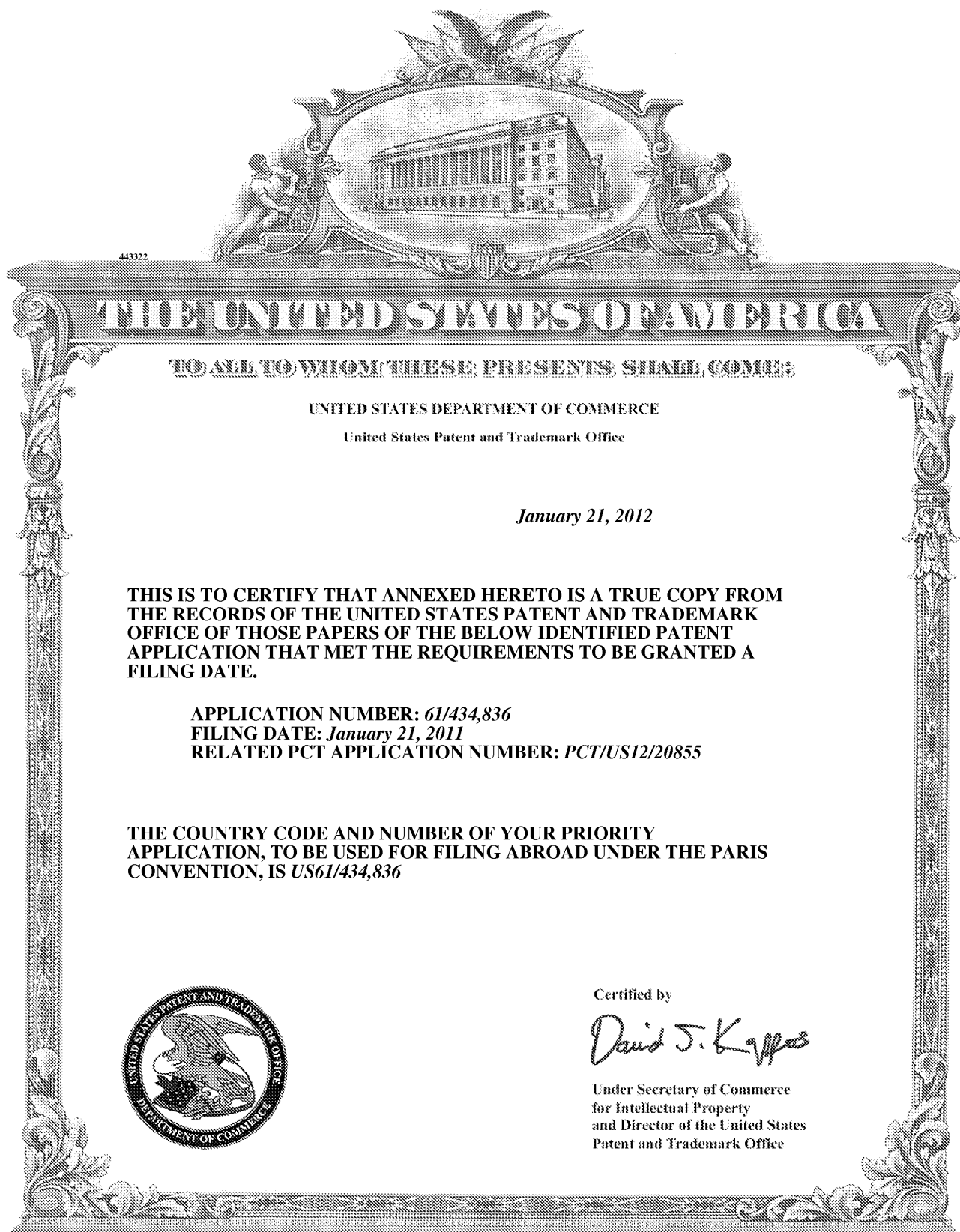


**DOCUMENT MADE AVAILABLE UNDER THE
PATENT COOPERATION TREATY (PCT)**

International application number:	PCT/US2012/020855
International filing date:	11 January 2012 (11.01.2012)
Document type:	Certified copy of priority document
Document details:	Country/Office: US
	Number: 61/434,836
	Filing date: 21 January 2011 (21.01.2011)
Date of receipt at the International Bureau:	22 January 2012 (22.01.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)



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 μ m compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

[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 funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy 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
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCAATTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAAACTTGTAACCGGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTGTAGCACCTTAAGTATAGATGGTGTAAACCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCC AAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTGAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
```

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

```
MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFISNATYKEIGLLTCEATVNGHLYKTNLYLTHRQNTIIDVVLSPSHGI
```

ELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEV
TCWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRWVSFLTTLHQLDNLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFVMSHEALHNHYTQKSLSLSPGK

[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-Fc Δ C1(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.

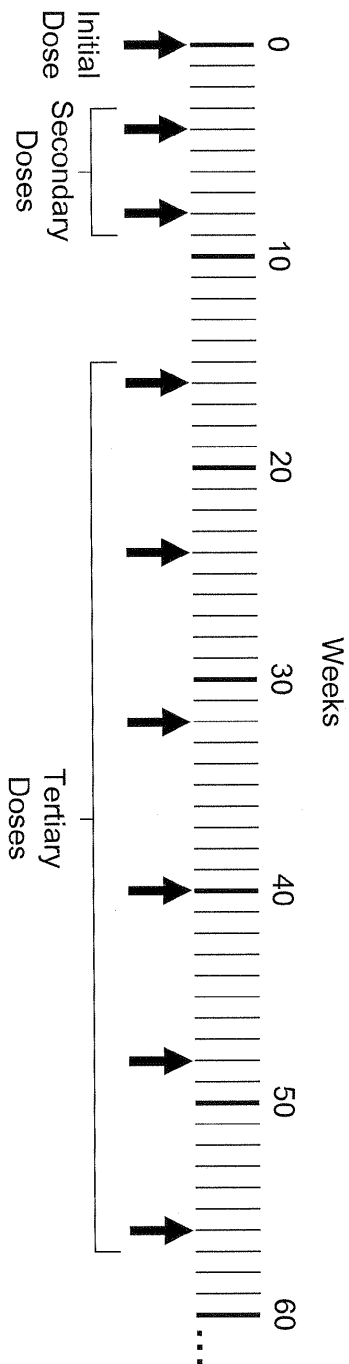


Figure 1

Doc Code: **TR.PROV**

Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

Approved for use through 09/30/2010 OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

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:	

Doc Code: **TR.PROV**

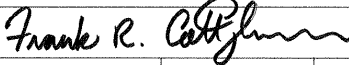
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

Approved for use through 09/30/2010 OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

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					
Warning Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.					
Signature Please see 37 CFR 1.4(d) for the form of the signature.					
Signature			Date (YYYY-MM-DD)	2011-01-20	
First Name	Frank	Last Name	Cottingham	Registration Number (If appropriate)	50437
This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.					

Electronic Acknowledgement Receipt	
EFS ID:	9276346
Application Number:	61434836
International Application Number:	
Confirmation Number:	3424
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	George D. Yancopoulos
Customer Number:	26693
Filer:	Frank Robert Cottingham
Filer Authorized By:	
Attorney Docket Number:	725P1
Receipt Date:	21-JAN-2011
Filing Date:	
Time Stamp:	08:13:01
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 220
RAM confirmation Number	7832
Deposit Account	180650
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Specification.pdf	1501900	yes	21
			8754fcd2ee5bfcd7d25055b8dc789e8b6e0da3e		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	18	
	Claims		19	20	
	Abstract		21	21	
Warnings:					
Information:					
2	Drawings-only black and white line drawings	Figure1.pdf	17039	no	1
			e47950cf51187db4ff832d06ed67c08a861a33c6		
Warnings:					
Information:					
3	Provisional Cover Sheet (SB16)	ProvAppCoverSheet.pdf	133277	no	2
			e5c5d4f9b241507299e72163bf60h682f18cae9		
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	29332	no	2
			f03219f50130dd6c073af7cd7c6427bec6c1c0e2		
Warnings:					
Information:					
Total Files Size (in bytes):			1681548		

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

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

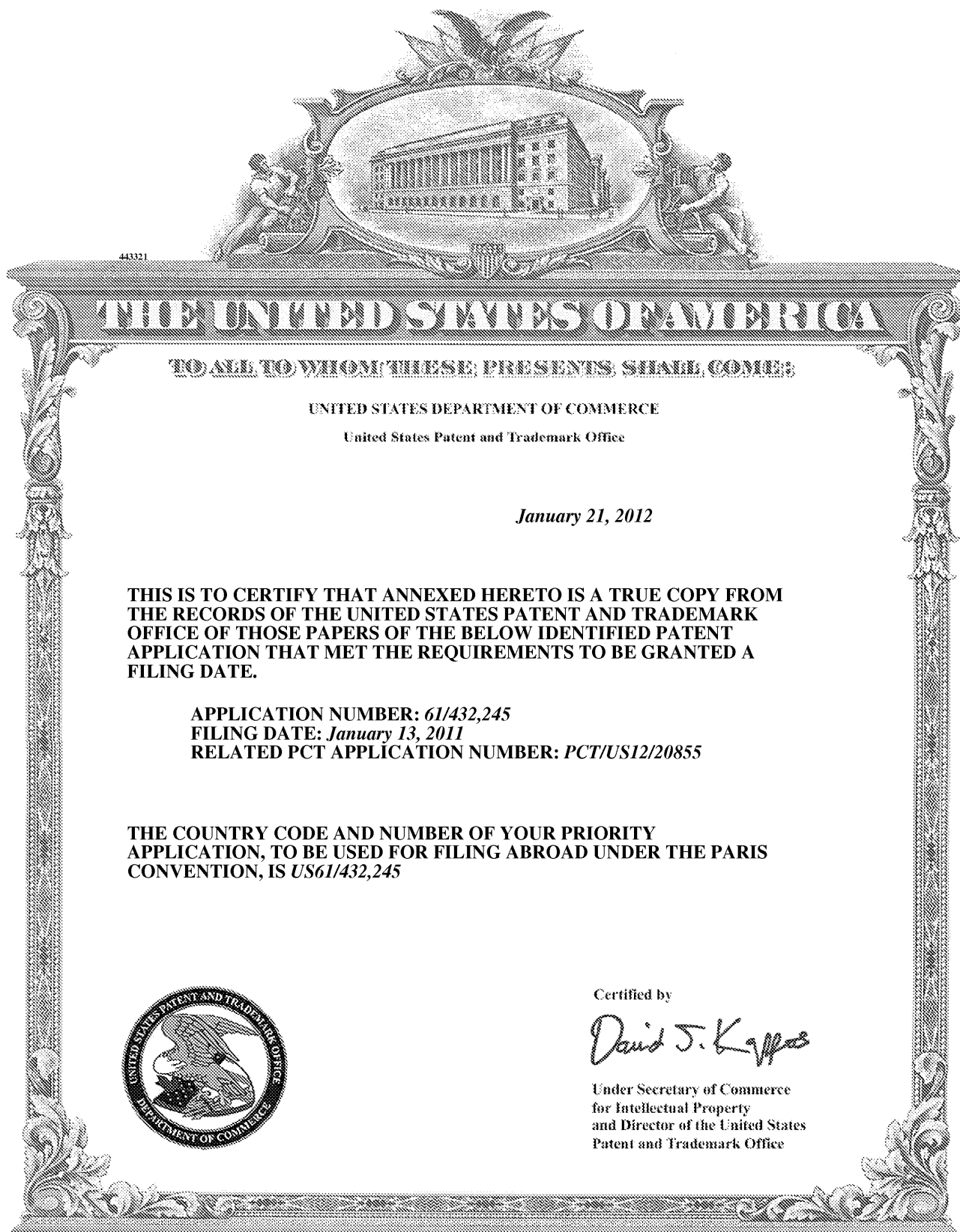
New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**DOCUMENT MADE AVAILABLE UNDER THE
PATENT COOPERATION TREATY (PCT)**

International application number:	PCT/US2012/020855
International filing date:	11 January 2012 (11.01.2012)
Document type:	Certified copy of priority document
Document details:	Country/Office: US
	Number: 61/432,245
	Filing date: 13 January 2011 (13.01.2011)
Date of receipt at the International Bureau:	22 January 2012 (22.01.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)



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 μ m compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

[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 funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy 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
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTACGTCACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCAATTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAAGGGCTTCATCATATCAAATGCAACGTACAAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGTCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAAACTTGTAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTGTAGCACCTTAAGTATAGATGGTGTAAACCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACATTTGTCAGGGTCCATGAAAAGGACA
AACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCT
TCCCCC AAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTGAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
```

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

```
MVS YWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLK
KFPLDTLIPDGKRIIWDSRKGFISNATYKEIGLLTCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGI
```

ELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEV
TCWVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRWVSFLTTLHQLDNLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFVMSHEALHNHYTQKSLSLSPGK

[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-Fc Δ C1(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.

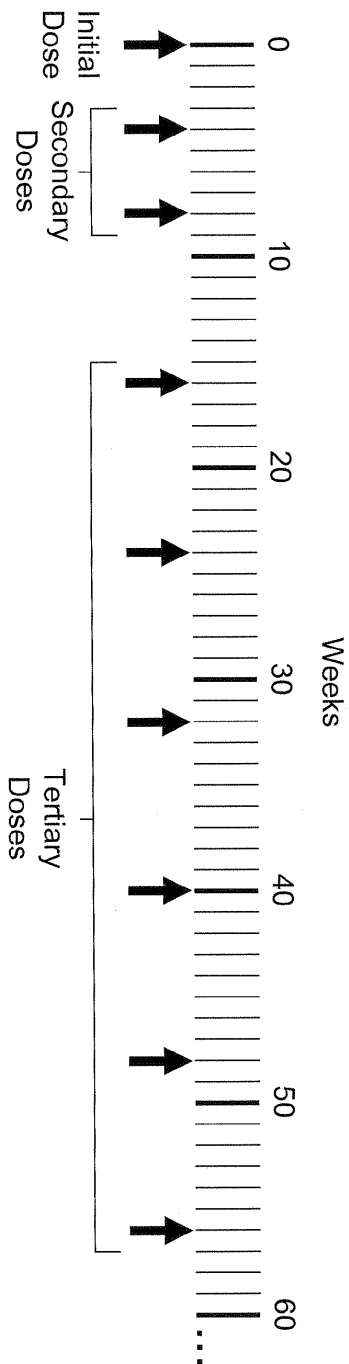


Figure 1

Doc Code: TR.PROV

Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

Approved for use through 09/30/2010 OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

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 i
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)		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:	

Doc Code: TR.PROV

Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

Approved for use through 09/30/2010 OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

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

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

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

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.

Electronic Acknowledgement Receipt	
EFS ID:	9221845
Application Number:	61432245
International Application Number:	
Confirmation Number:	2914
Title of Invention:	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
First Named Inventor/Applicant Name:	. .
Customer Number:	26693
Filer:	Frank Robert Cottingham
Filer Authorized By:	
Attorney Docket Number:	725P
Receipt Date:	13-JAN-2011
Filing Date:	
Time Stamp:	11:06:57
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 220
RAM confirmation Number	7877
Deposit Account	180650
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Specification.pdf	1502821 0e6dfc1d69849494c1e0a9e5f9c870da99736	yes	21
Multipart Description/PDF files in .zip description					
	Document Description		Start	End	
	Specification		1	18	
	Claims		19	20	
	Abstract		21	21	
Warnings:					
Information:					
2	Drawings-only black and white line drawings	Figure1.pdf	17083 d38cd6a62eaed04c5b9dab783c71ae7ab0351ef	no	1
Warnings:					
Information:					
3	Provisional Cover Sheet (SB16)	Provisional_Cover_Sheet.pdf	131021 069e87e1c37979a56defafae021194h588ba2b99a	no	2
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	29246 d50a4652d93e1899e475e874c4f8c03786cd26d2	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			1680171		

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

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

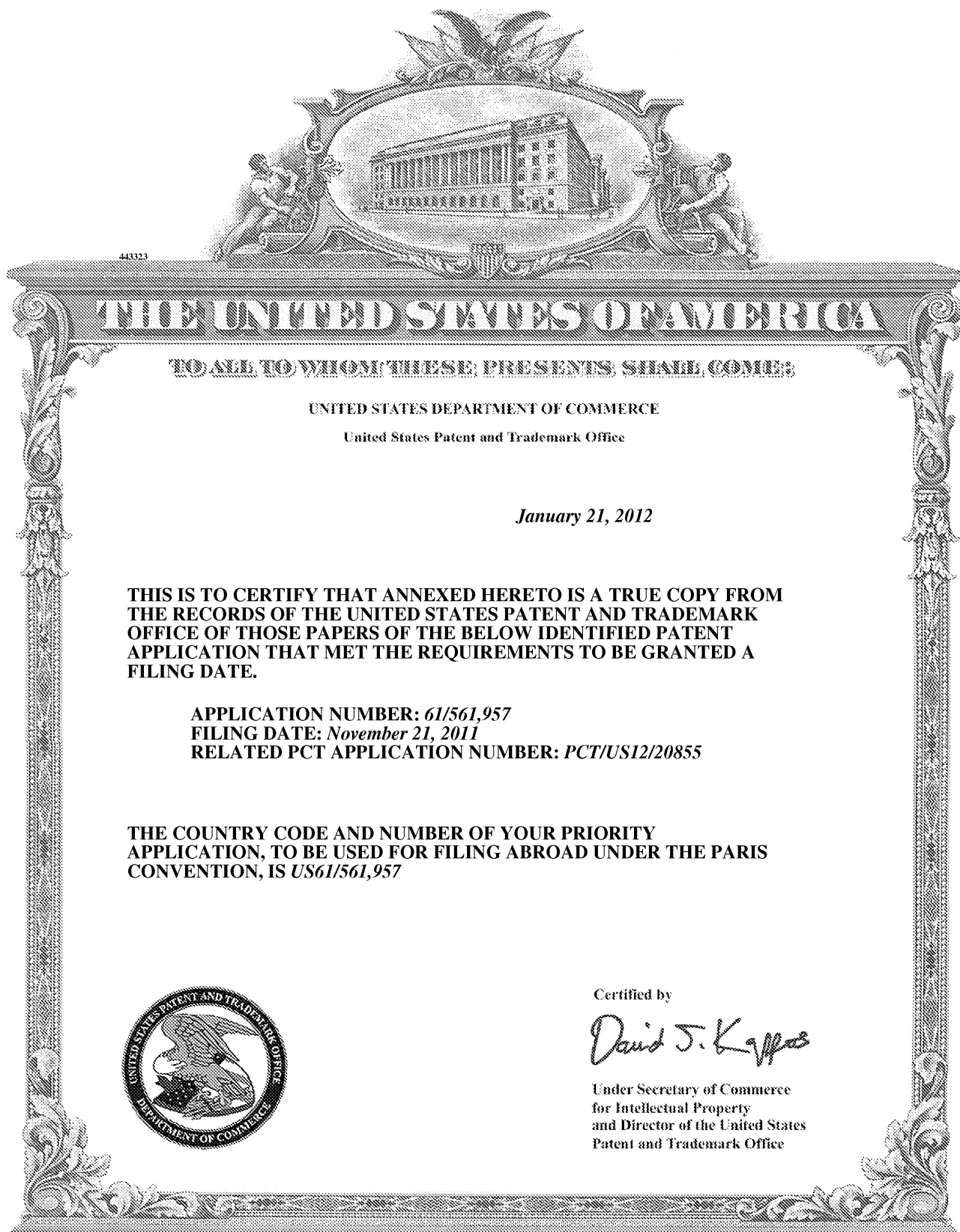
New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**DOCUMENT MADE AVAILABLE UNDER THE
PATENT COOPERATION TREATY (PCT)**

International application number:	PCT/US2012/020855
International filing date:	11 January 2012 (11.01.2012)
Document type:	Certified copy of priority document
Document details:	Country/Office: US
	Number: 61/561,957
	Filing date: 21 November 2011 (21.11.2011)
Date of receipt at the International Bureau:	22 January 2012 (22.01.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)



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 μ m compared to the lowest previous value as measured by optical coherence tomography (OCT); or (ii) a loss from the best previous letter score of at least 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; or (iii) new or persistent fluid as indicated by OCT; or (iv) new onset classic neovascularization, or new or persistent leak on fluorescein angiography (FA); or (v) new macular hemorrhage; or (vi) 12 weeks have elapsed since the previous injection. According to the present protocol, subjects must receive an injection at least every 12 weeks.

[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 funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy 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 $-413.0 \mu\text{m}$ for VEGFT-treated patients vs $-381.8 \mu\text{m}$ for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

[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):

```
ATGGTCAGCTACTGGGACACCGGGTCCTGCTGTGCGCGCTGCTCAGCTGTCTGCTTCTCAC
AGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTTCGTAGAGATGTACAGTGAAATCCCCGA
AATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTTACGTACCTAACAT
CACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGCATAATCTGG
GACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGCTTCTGACCTGT
GAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGACAAACCAATACAA
TCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGGAGAAAAGCTTGCTT
AAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACTGGGAATACCCTTCTTCG
AAGCATCAGCATAAGAACTTGTAAACCGAGACCTAAAAACCCAGTCTGGGAGTGAGATGAAG
AAATTTTTTGAGCACCTTAAGTATAGATGGTGTAAACCGGAGTGACCAAGGATTGTACACCTGTG
CAGCATCCAGTGGGCTGATGACCAAGAAGAAGCAGCACATTTGTCAGGGTCCATGAAAAGGACA
AACTCACACATGCCACCGTGCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTCT
TCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTGAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAATGA
```

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

```
MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIHMTEGRELVIPCRVTSNITVTLK
KFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLTHRQTNTIIDVLSPSHG
ELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS
DQGLYTCAASSGLMTKKNSTFVRVHEKDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
```

[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.

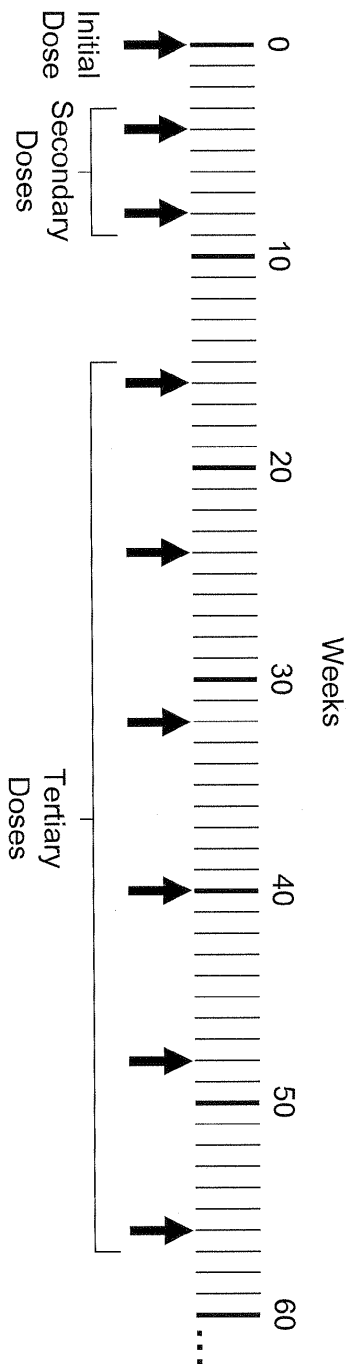


Figure 1

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.		
☒ 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		
TOTAL FEE AMOUNT (\$) 250		

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 10 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PROVISIONAL APPLICATION COVER SHEET
Page 2 of 2

PTO/SB/16 (09-11)

Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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: _____	

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

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	
EFS ID:	11448343
Application Number:	61561957
International Application Number:	
Confirmation Number:	8366
Title of Invention:	Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders
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

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 250
RAM confirmation Number	8604
Deposit Account	180650
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		725P2_Specification.pdf	9674698	yes	22
			8932a1db1ea887d8e2c965fc9ea489dd56c890e		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	19	
	Claims		20	21	
	Abstract		22	22	
Warnings:					
Information:					
2	Drawings-only black and white line drawings	Figure1.pdf	17039	no	1
			945457aa6d8cc57408afb159b29373a0f0bae1c		
Warnings:					
Information:					
3	Provisional Cover Sheet (SB16)	725P2_ProvCoverSheet.pdf	734671	no	2
			7251b0bdefc0ab0f858f53ff5047fc718aa480cd5		
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29001	no	2
			114875c4ced6b5dab480d1d1108b64260da06ed		
Warnings:					
Information:					
Total Files Size (in bytes):			10455409		

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

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

J A • K E M P

BY ONLINE FILING

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

28 April 2017

NEW DIVISIONAL APPLICATION

Dear Sirs

New European Patent Application
divided out of European Patent Application No. 12700590.8
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP-A DXP/mqr

We are filing herewith a new European patent application divided out of European Patent Application No. 12700590.8. We enclose the following documents:

- 1 A Request Form.
- 2 A Designation of Inventor Form for the inventor.
- 3 A description, claims, abstract, Figures and sequence listing to form the basis of this new divisional application.
- 4 A copy of the International Search Report issued by the European Patent Office in respect of the parent application.
- 5 An annotated version of the claims of the divisional indicating in bold the basis for each claim in the parent application as filed.

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

- the online filing fee (120 EUR);
- the search fee (1300 EUR); and
- the third to sixth year renewal fees (470, 585, 820 and 1050 EUR).

We request that any underpayment is deducted from, or any overpayment is credited to, deposit account 2805.0038.

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7430 1000
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

We wish the enclosed text to form the basis of the divisional application. This text is identical to that of the parent application as originally filed except for amendment of the claims and the introduction of a "Further Numbered Embodiments of the Invention" section at the end of the description. The new claims find basis in the originally filed parent application as indicated in the annotated version of the claims provided. The further numbered embodiments of the invention correspond to the original claims of the parent application.

The subject matter covered by the claims of this divisional application is related to that of the original claims of the parent application, European Patent Application No. 12700590.8 which was searched by the European Patent Office in the International phase, PCT Application No. PCT/US2012/020855. We therefore request a refund of the search fee paid on the divisional application in accordance with Article 9(2) of the Rules Relating to Fees.

The European Patent Office is requested to place a copy of the priority applications namely US 61/432,245 filed 13 January 2011, US 61/434,836 filed 21 January 2011 and US 61/561,957 filed 21 November 2011 from the parent application no. 12700590.8 onto the file of this divisional application.

We request that electronic version of the sequence listing filed at the European Patent Office in connection with European Application No. 12700590.8 be transferred to the file for this divisional application. A copy of the sequence listing forming part of the divisional application as filed is also now provided. We confirm that, to the best of our knowledge and belief, the sequence listing does not include matter that goes beyond the content of the parent application as filed. Indeed, the attached sequence listing is identical to that present in the parent application as filed.

Yours faithfully

Electronically Signed
DR DAVID POWER
AUTHORISED REPRESENTATIVE



Request for grant of a European patent

<i>For official use only</i>		
1 Application number:	MKEY	MKEY - EP17168808.8
2 Date of receipt (Rule 35(2) EPC):	DREC	DREC - 28 Apr 2017
3 Date of receipt at EPO (Rule 35(4) EPC):	RENA	
4 Date of filing:		

5 Grant of European patent, and examination of the application under Article 94, are hereby requested. ☒

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

Procedural language:

en

Description and/or claims filed in:

en

6 Applicant's or representative's reference

N400458EP-A

Filing Office:

EP

Applicant 1

7-1

Name:

Regeneron Pharmaceuticals, Inc.

8-1

Address:

777 Old Saw Mill River Road
Tarrytown NY New York NY 10591
United States of America

10-1

State of residence or of principal place of business:

United States of America

14.1 The/Each applicant hereby declares that he is an entity or a natural person under Rule 6(4) EPC. ☐

Representative 1

15-1

Name:

POWER, Mr David

Company:

J A Kemp

16-1

Address of place of business:

14 South Square
Gray's Inn
London Greater London WC1R 5JJ
United Kingdom

17-1

Telephone:

+44 20 3077 8600

17-1

Fax:

+44 20 7430 1000

17-1

E-mail:

mail@jakemp.com

Inventor(s)

23 Inventor details filed separately



24 Title of invention

Title of invention:

USE OF A VEGF ANTAGONIST TO TREAT
ANGIOGENIC EYE DISORDERS**25 Declaration of priority (Rule 52)**

A declaration of priority is hereby made for the following applications

	State	Filing date	Kind	Application number:	Search results under Rule 141(1) are attached
Priority 01	US	13.01.2011	pr	61/432245	☐
Priority 02	US	21.01.2011	pr	61/434836	☐
Priority 03	US	21.11.2011	pr	61/561957	☐

25.2 This application is a complete translation of the previous application



25.3 It is not intended to file a (further) declaration of priority

**26 Reference to a previously filed application****27 Divisional application**

Application number of earlier application:

EP12700590.8

Date of Filing (Art. 80/Rule 40 EPC):

11 January 2012

27.1 This divisional application is of the following generation:



1



2



3



4



5 or subsequent

28 Article 61(1)(b) application**29 Claims**

Number of claims:

13

29.1



as attached

29.2



as in the previously filed application (see Section 26.2)

29.3



The claims will be filed later

30 Figures

It is proposed that the abstract be published together with figure No.

31 Designation of contracting states

All the contracting states party to the EPC and valid for the parent application at the time of filing of this divisional application are deemed to be designated (see Article 76(2)).

32 Different applicants for different contracting states

33 Extension/Validation

This application is deemed to be a request to extend the effects of the European patent application and the European patent granted in respect of it to all non-contracting states to the EPC with which extension or validation agreements are in force on the date on which the application is filed. However, the request is deemed withdrawn if the extension fee or the validation fee, whichever is applicable, is not paid within the prescribed time limit.

33.1 It is intended to pay the extension fee(s) for the following state(s):

33.2 It is intended to pay the validation fee(s) for the following state(s):

34 Biological material

38 Nucleotide and amino acid sequences

The European patent application contains a sequence listing as part of the description

☒

The sequence listing is attached in computer-readable format in accordance with WIPO Standard ST.25

☒

The sequence listing is attached in PDF format

☐

38.3 The Office is requested to add to the dossier on the European patent application, in electronic form and for search purposes only (i.e. not as part of the description), a copy of the Standard-compliant sequence listing filed for the earlier application mentioned in Section 27. It is hereby declared that the sequence listing does not extend beyond the content of the divisional application as originally filed.

☒

Further indications

39 Additional copies of the documents cited in the European search report are requested

Number of additional sets of copies:

40 Refund of the search fee under to Article 9 of the Rules relating to Fees is requested

☒

Application or publication number of earlier search report:

12700590.8

42 Payment

Mode of payment

Debit from deposit account

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

Currency: **EUR**

Deposit account number: **28050038**

Account holder: **J A Kemp**

43 Refunds

Fees	Factor applied	Fee schedule	Amount to be paid
001 Filing fee - EP direct - online	1	120.00	120.00
002 Fee for a European search - Applications filed on/after 01.07.2005	1	1 300.00	1 300.00
015 Claims fee - For the 16th to the 50th claim	0	235.00	0.00
015e Claims fee - For the 51st and each subsequent claim	0	585.00	0.00
033 Renewal fee for the 3rd year	1	470.00	470.00
034 Renewal fee for the 4th year	1	585.00	585.00
035 Renewal fee for the 5th year	1	820.00	820.00
036 Renewal fee for the 6th year	1	1 050.00	1 050.00
501 Additional filing fee for the 36th and each subsequent page	0	15.00	0.00
Total:		EUR	4 345.00

44-A Forms

Details:

System file name:

A-1	Request	as ep-request.pdf
A-2	1. Designation of inventor	1. Inventor as f1002-1.pdf

44-B Technical documents

Original file name:

System file name:

B-1	Specification	Spec as filed May17 N400458EP-A DXP.pdf Description; 13 claims; 1 figure(s); abstract	SPECEPO-1.pdf
B-2	Sequence listings, ASCII	Sequence listing N400458EP-A DXP.txt	SEQLTXT.txt
B-3	Pre-conversion archive	Preconversion N400458EP-A DXP.zip	OLF-ARCHIVE.zip

44-C Other documents

Original file name:

System file name:

C-1	ISR on Parent Application	ISR on Parent application N400458EP-A DXP.pdf	OTHER-1.pdf
------------	---------------------------	---	-------------

C-2	Claims showing basis	Divisional claims with basis N400458EP-A DXP.PDF	OTHER-2.PDF
C-3	Covering letter	Divisional filing letter N400458EP-A DXP.pdf	OTHER-3.pdf

45

General authorisation:

46 Signature(s)

Place: London

Date: 28 April 2017

Signed by: David Power 23473

Representative name: David POWER

Capacity: (Representative)

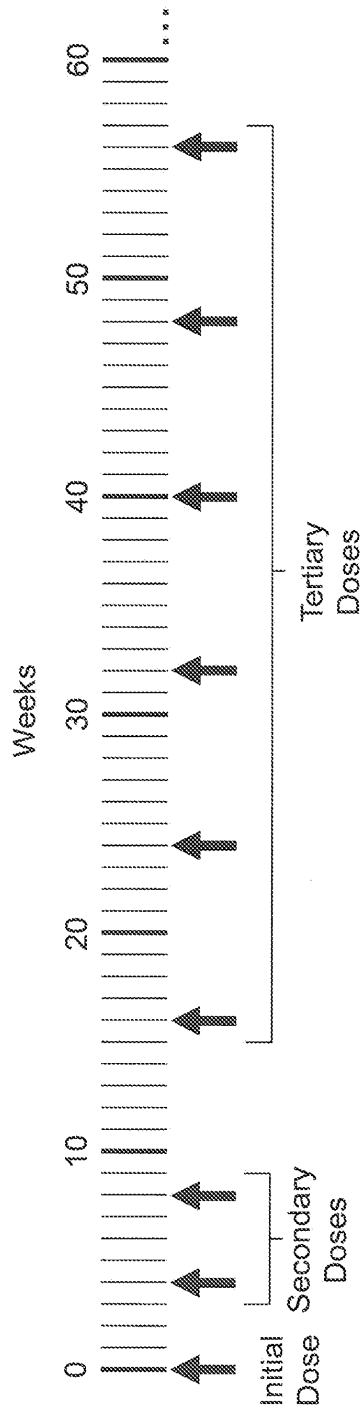


Figure 1

Form 1002 - 1: Public inventor(s)

Designation of inventor

User reference: N400458EP-A
Application No:

Public

	Inventor	Name:	YANCOPOULOS George D
		Address:	1519 Baptist Church Road Yorktown Heights NY New York 10598 United States of America
		The applicant has acquired the right to the European patent:	Under agreement:

Signature(s)

Place: London
Date: 28 April 2017
Signed by: David Power 23473
Representative name: David POWER
Capacity: (Representative)

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-Fc Δ C1(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 – 179 μ)] on optical coherence tomography (OCT) was reduced from 119 μ to 27 μ as assessed by Fast Macular Scan and from 194 μ to 60 μ 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 135 μ , $p < 0.0001$). 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, juxtasceral 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 funduscopy examination, fundus photography and FA. At the Screen Visit (Visit 1) funduscopy 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 $-413.0 \mu\text{m}$ for VEGFT-treated patients vs $-381.8 \mu\text{m}$ for sham-treated patients. The proportion of patients with ocular neovascularization at Week 24 were 0% for VEGFT-treated patients and 6.8% for sham-treated patients, respectively; at Week 52 after receiving VEGFT PRN, proportions were 0% and 6.8% for VEGFT-treated and sham-treated. At Week 24, the mean change from baseline in the VFQ-25 total score was 7.2 vs 0.7 for the VEGFT-treated and sham-treated groups; at Week 52, the scores were 7.5 vs 5.1 for the VEGFT-treated and sham-treated groups.

[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
ACAGGATCTAGTTCCGGAAGTGATACCGGTAGACCTTTCGTAGAGATGTACAGTGAATCC
CCGAAATTATACACATGACTGAAGGAAGGGAGCTCGTCATTCCCTGCCGGGTACGTCAC
CTAACATCACTGTTACTTTAAAAAAGTTTCCACTTGACACTTTGATCCCTGATGGAAAACGC
ATAATCTGGGACAGTAGAAAGGGCTTCATCATATCAAATGCAACGTACAAAGAAATAGGGC
TTCTGACCTGTGAAGCAACAGTCAATGGGCATTTGTATAAGACAAACTATCTCACACATCGA
CAAACCAATACAATCATAGATGTGGTTCTGAGTCCGTCTCATGGAATTGAACTATCTGTTGG
AGAAAAGCTTGTCTTAAATTGTACAGCAAGAACTGAACTAAATGTGGGGATTGACTTCAACT
GGGAATACCCTTCTTGAAGCATCAGCATAAGAACTTGTAACCGAGACCTAAAAACCCA
GTCTGGGAGTGAGATGAAGAAATTTTGGACACCTTAAGTATAGATGGTGTAAACCCGGAGT
GACCAAGGATTGTACACCTGTGCAGCATCCAGTGGGCTGATGACCAAGAAGAACAGCACA
TTTGTACAGGGTCCATGAAAAGGACAAAACCTCACACATGCCCACCGTGCCCAGCACCTGAA
CTCCTGGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATC
TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG
AGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
```

GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCG
AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
CATCCCGGGATGAGCTGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGAGAACAACACTACAAG
ACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCCTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

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

MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITV
TLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYLTHRQNTIIDVLS
PSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRDLKTQSGSEMKKFLSTLT
IDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKHTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNQKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQ
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.

Further Numbered Embodiments of the Invention:

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

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

2. The method of item 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

3. The method of item 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

4. The method of item 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

5. The method of item 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

6. The method of item 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.

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

8. The method of item 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.

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

10. The method of item 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

11. The method of item 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

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

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

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

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

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

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

18. The method of item 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

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

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

21. A VEGF antagonist for use in a method of treating an angiogenic eye disorder in a patient, wherein the method comprises sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

22. The VEGF antagonist of item 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

23. The VEGF antagonist of item 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. The VEGF antagonist of any one of items 21 to 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. The VEGF antagonist of any one of items 21 to 23, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. The VEGF antagonist of any one of items 21 to 25, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization.

27. The VEGF antagonist of item 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. The VEGF antagonist of any one of items 21 to 27, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule.

29. The VEGF antagonist of item 28, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule.

30. The VEGF antagonist of item 29, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

31. The VEGF antagonist of item 29, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

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

33. The VEGF antagonist of item 32, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

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

35. The VEGF antagonist of item 34, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

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

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

SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.

<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

<151> 2011-01-13

<150> 61/434,836

<151> 2011-01-21

<150> 61/561,957

<151> 2011-11-21

<160> 2

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 1377

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 1

atgggtcagct	actggggacac	cggggtcctg	ctgtgcgcg	tgctcagctg	tctgcttctc	60
acaggatcta	gttcgggaag	tgataccggt	agacctttcg	tagagatgta	cagtgaatc	120
cccgaatta	tacacatgac	tgaaggaagg	gagctcgta	ttccctgccg	ggttacgtca	180
cctaaccatca	ctgttacttt	aaaaaagttt	ccacttgaca	ctttgatccc	tgatggaaaa	240
cgcataatct	gggacagtag	aaagggcttc	atcatatcaa	atgcaacgta	caaagaaata	300
gggcttctga	cctgtgaagc	aacagtcaat	gggcatttgt	ataagacaaa	ctatctcaca	360
catcgacaaa	ccaatacaat	catagatgtg	gttctgagtc	cgtctcatgg	aattgaacta	420
tctgtttggag	aaaagcttgt	cttaaattgt	acagcaagaa	ctgaactaaa	tgtggggatt	480
gacttcaact	gggaataccc	ttcttcgaag	catcagcata	agaaacttgt	aaaccgagac	540
ctaaaaaccc	agtctgggag	tgagatgaag	aaatttttga	gcaccttaac	tatagatggt	600
gtaacccgga	gtgaccaagg	attgtacacc	tgtgcagcat	ccagtgggct	gatgaccaag	660
aagaacagca	catttgtcag	ggtccatgaa	aaggacaaaa	ctcacacatg	cccaccgtgc	720
ccagcacctg	aactcctggg	gggaccgtca	gtcttcctct	tccccccaaa	acccaaggac	780
accctcatga	tctcccgga	ccctgaggtc	acatgcgtgg	tggtggacgt	gagccacgaa	840
gaccctgagg	tcaagttcaa	ctggtacgtg	gacggcgtgg	aggtgcataa	tgccaagaca	900
aagccgcggg	aggagcagta	caacagcacg	taccgtgtgg	tcagcgtcct	caccgtcctg	960
caccaggact	ggctgaatgg	caaggagtac	aagtgcaagg	tctccaacaa	agccctccca	1020
gcccccatcg	agaaaacccat	ctccaaagcc	aaagggcagc	cccagagaac	acaggtgtac	1080
accctgcccc	catcccgga	tgagctgacc	aagaaccagg	tcagcctgac	ctgcctggtc	1140
aaaggcttct	atcccagcga	catcgccgtg	gagtgaggaga	gcaatgggca	gccgggagaac	1200
aactacaaga	ccacgcctcc	cgtgctggac	tccgacggct	ccttcttctc	ctacagcaag	1260
ctcaccgtgg	acaagagcag	gtggcagcag	gggaacgtct	tctcatgctc	cgtgatgcat	1320
gaggtctctg	acaaccacta	cacgcagaag	agcctctccc	tgtctccggg	taaatga	1377

<210> 2

<211> 458

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 2

```

Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1      5      10      15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
      20      25      30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
      35      40      45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
      50      55      60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65      70      75      80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
      85      90      95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
      100      105      110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
      115      120      125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
130      135      140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
145      150      155      160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
      165      170      175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
      180      185      190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
      195      200      205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
210      215      220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225      230      235      240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
      245      250      255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
      260      265      270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
      275      280      285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
290      295      300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305      310      315      320
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
      325      330      335
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
      340      345      350
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
      355      360      365
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
      370      375      380
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385      390      395      400
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
      405      410      415
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
      420      425      430
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
      435      440      445
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450      455

```

CLAIMS

1. A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and

wherein the VEGF antagonist comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

2. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is age related macular degeneration.

3. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic retinopathy.

4. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic macular edema.

5. The VEGF antagonist for according to claim 1, wherein the angiogenic eye disorder is central retinal vein occlusion.

6. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is corneal neovascularization.

7. The VEGF antagonist for use according to any one of the preceding claims, wherein the VEGF antagonist comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

8. The VEGF antagonist for use according to any one of the preceding claims, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

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

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

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

12. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

13. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

CLAIMS WITH SUMMARY OF BASIS

1. A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and

wherein the VEGF antagonist comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1. **[Basis - Original Parental claims 1, 5, 6 and 9]**

2. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is age related macular degeneration. **[Basis - Original Parental claims 6 and 7 and Paragraph [0006]]**

3. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic retinopathy. **[Basis - Original Parental claim 6 and Paragraph [0006]]**

4. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic macular edema. **[Basis - Original Parental claim 6 and Paragraph [0006]]**

5. The VEGF antagonist for according to claim 1, wherein the angiogenic eye disorder is central retinal vein occlusion. **[Basis - Original Parental claim 6 and Paragraph [0006]]**

6. The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is corneal neovascularization. **[Basis - Original Parental claim 6 and Paragraph [0006]]**

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. **[Basis - Original Parental claim 11 and paragraph [0023]]**

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. **[Basis - Original Parental claims 12 and 13]**

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. **[Basis - Original Parental claim 13]**

10. The VEGF antagonist for use according to claim 9, wherein the intraocular administration is intravitreal administration. **[Basis - Original Parental claims 14]**

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. **[Basis - Original Parental claim 18]**

12. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist. **[Basis - Original Parental claim 19]**

13. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist. **[Basis - Original Parental claim 20]**

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_gry_save=&p_subtitle=Biomedical%20Literature%20List&p_dailys=N&p_tsearch=A&p_text=N&p_whatToShow=REF&p_prouQuantity=5&p_page=10#link [retrieved on 2012-04-18] the whole document ----- -/--	1-37



Further documents are listed in the continuation of Box C.



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

"Z" document member of the same patent family

Date of the actual completion of the international search

19 April 2012

Date of mailing of the international search report

22/05/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Rodrigo-Simón, Ana

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

page 1 of 3

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 127

Samsung Bioepis Exhibit 1067, pg. 127

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/020855

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NGUYEN Q D ET AL: "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration", OPTHALMOLOGY, J. B. LIPPINCOTT CO., PHILADELPHIA, PA, US, vol. 116, no. 11, 1 November 2009 (2009-11-01), pages 2141-2148.E1, XP026732998, ISSN: 0161-6420, DOI: 10.1016/J.OPHTHA.2009.04.030 [retrieved on 2009-08-22] abstract page 2142, column 1 - paragraph 3 page 2147, column 1, paragraph 2	1-37
A	US 2007/190058 A1 (SHAMS NAVEED [US]) 16 August 2007 (2007-08-16) claim 1 paragraph [0112] page 12, paragraph 111	1-37
A	US 2006/172944 A1 (WIEGAND STANLEY J [US] ET AL) 3 August 2006 (2006-08-03) paragraphs [0008], [0017] claims 1,2	1-37
A	US 2005/163798 A1 (PAPADOPOULOS NICHOLAS J [US] ET AL) 28 July 2005 (2005-07-28) claim 65 paragraph [0122]	1-37
A	WO 00/75319 A1 (REGENERON PHARMA [US]; PAPADOPOULOS NICHOLAS J [US]; DAVIS SAMUEL [US]) 14 December 2000 (2000-12-14) page 87, line 14 - line 88 page 14, line 7 - line 12	1-37
A	US 2006/058234 A1 (DALY THOMAS J [US] ET AL) 16 March 2006 (2006-03-16) paragraph [0067] claim 23 page 2, paragraph 15	1-37
A	US 2005/260203 A1 (WIEGAND STANLEY J [US] ET AL) 24 November 2005 (2005-11-24) page 7; example 8 page 8; example 9 page 8; example 11 page 9; example 2	1-37
	----- -/--	

1

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

page 2 of 3

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 128

Samsung Bioepis Exhibit 1067, pg. 128

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/020855

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DO DV ET AL.: "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema.", BR J OPHTHALMOL, vol. 93, no. 2, February 2009 (2009-02), pages 144-1449, XP009158490, abstract page 149, paragraph 2 -----	1-37
A	ANANT PAI ET AL.: "Current concepts in intravitreal drug therapy for diabetic retinopathy", SAUDI JOURNAL OF OPHTHALMOLOGY, vol. 24, no. 4, 30 June 2010 (2010-06-30), pages 143-149, XP002674122, page 147, paragraph 4 -----	1-37
X,P	DO DIANA V ET AL: "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema.", OPHTHALMOLOGY SEP 2011 LNKD-PUBMED:21546089, vol. 118, no. 9, September 2011 (2011-09), pages 1819-1826, XP002674123, ISSN: 1549-4713 the whole document -----	1-37
T	STEWART MW.: "The expanding role of vascular endothelial growth factor inhibitors in ophthalmology", MAYO CLIN PROC, vol. 87, no. 1, January 2012 (2012-01), pages 77-88, XP002674124, the whole document -----	
A	anonymous: "LUCENTIS® (ranibizumab injection) Intravitreal Injection", June 2006 (2006-06), pages 1-3, XP002674125, Retrieved from the Internet: URL:http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf [retrieved on 2012-04-18] page 1, column 1, line 20 - page 1, column 2, line 9 -----	1-37

1

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

page 3 of 3

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 129

Samsung Bioepis Exhibit 1067, pg. 129

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/020855

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007190058 A1	16-08-2007	NONE	
US 2006172944 A1	03-08-2006	US 2006172944 A1	03-08-2006
		US 2008085276 A1	10-04-2008
US 2005163798 A1	28-07-2005	US 7070959 B1	04-07-2006
		US 2005163798 A1	28-07-2005
		US 2005175610 A1	11-08-2005
		US 2005245447 A1	03-11-2005
		US 2008194460 A1	14-08-2008
		US 2008194799 A1	14-08-2008
		US 2008220004 A1	11-09-2008
		US 2009081217 A1	26-03-2009
		US 2009155899 A1	18-06-2009
		US 2010221782 A1	02-09-2010
		US 2011028698 A1	03-02-2011
		US 2012064621 A1	15-03-2012
WO 0075319 A1	14-12-2000	AT 293164 T	15-04-2005
		AT 417928 T	15-01-2009
		AU 779303 B2	13-01-2005
		AU 5040400 A	28-12-2000
		BR 0011407 A	02-04-2002
		CA 2376379 A1	14-12-2000
		CN 1369009 A	11-09-2002
		CN 101433715 A	20-05-2009
		CZ 20014387 A3	16-10-2002
		DE 60019415 D1	19-05-2005
		DE 60019415 T2	09-03-2006
		DK 1544299 T3	23-03-2009
		EP 1183353 A1	06-03-2002
		EP 1544299 A1	22-06-2005
		ES 2237429 T3	01-08-2005
		ES 2319305 T3	06-05-2009
		HK 1043388 A1	10-06-2005
		HR 20010908 A2	30-04-2005
		HU 0201515 A2	28-08-2002
		IL 146890 A	08-07-2008
		JP 4723140 B2	13-07-2011
		JP 2003501089 A	14-01-2003
		JP 2011024595 A	10-02-2011
		MX PA01012630 A	22-07-2002
		NO 20016036 A	08-02-2002
		NZ 515913 A	30-01-2004
		PL 352246 A1	11-08-2003
		PT 1183353 E	30-06-2005
		PT 1544299 E	18-03-2009
		SK 17522001 A3	01-04-2003
		WO 0075319 A1	14-12-2000
		ZA 200110068 A	06-12-2002
US 2006058234 A1	16-03-2006	NONE	
US 2005260203 A1	24-11-2005	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)



Acknowledgement of receipt

We hereby acknowledge receipt of your request for grant of a European patent as follows:

Submission number	5239632	
Application number	EP17168808.8	
File No. to be used for priority declarations	EP17168808	
Date of receipt	28 April 2017	
Your reference	N400458EP-A	
Applicant	Regeneron Pharmaceuticals, Inc.	
Country	US	
Title	USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS	
Documents submitted	package-data.xml application-body.xml SPECEPO-1.pdf\Spec as filed May17 N400458EP-A DXP.pdf (26 p.) SEQLTXT.txt\Sequence listing N400458EP-A DXP.txt OTHER-2.PDF\Divisional claims with basis N400458EP-A DXP.PDF (3 p.) f1002-1.pdf (1 p.)	ep-request.xml ep-request.pdf (5 p.) OLF-ARCHIVE.zip\Preconversion N400458EP-A DXP.zip OTHER-1.pdf\ISR on Parent application N400458EP-A DXP.pdf (4 p.) OTHER-3.pdf\Divisional filing letter N400458EP-A DXP.pdf (2 p.)
Submitted by	CN=David Power 23473	
Method of submission	Online	

Acknowledgement of receipt - application number EP17168808.8

Page 1 of 2

Date and time
receipt generated

28 April 2017, 16:16 (CEST)

Message Digest

AC:7C:96:A8:1E:06:C2:3C:91:C0:01:20:06:83:C9:A1:73:D3:EC:67

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/

ABSTRACT

Use of a VEGF antagonist to treat angiogenic eye disorders

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.

J A • K E M P

FAX

Sent to Fax No: +49 89 2399 4465
2 Pages

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

ATTENTION: CLAUDIA WEBER, LEGAL DIVISION

06 June 2017

PLEASE SEE ACCOMPANYING PAGES

Please acknowledge safe and complete receipt of this transmission

SIGNED

DATE:

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • MUNICH
14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7430 1000
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

Duration: 06.06.2017 15:18:51 - 06.06.2017 15:19:21. This page 1 of 2 was completed at 06.06.2017 15:19:01

Received at the EPO on Jun 06, 2017 15:19:21. Page 1 of 2

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 134

Samsung Bioepis Exhibit 1067, pg. 134

J A • KEMP

BY FAX

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

ATTENTION: CLAUDIA WEBER, LEGAL DIVISION

06 June 2017

Dear Ms Weber

**Registration of J A Kemp as an association of professional representatives
- Association No. 811**

J A Kemp has been registered as an association of professional representatives under the no. 811 with effect from 24 May 2017.

I request that all the live European cases on the EPO's records, in which the professional representative is an EP attorney from J A Kemp, be transferred to the newly registered association (J A Kemp - Association No. 811). A listing of the current members of the association was sent to me by the Legal and Unitary Patent Division by letter of 30 May 2017. If you need a copy of that letter please let me know.

I confirm that this is to include both pending European patent application and oppositions.

My understanding is that this transfer would normally trigger the issue of a hard copy EPO form on each affected case. We do not wish to receive an individual notification on each case affected. Please would you suppress the issue of those individual notification and instead simply send us one single listing of the cases affected.

We currently receive Communications on our EP cases via the EPO's Mailbox service. We wish this to continue.

Yours faithfully

Electronically Signed

NIGEL PRICE

J A KEMP

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ

T +44 20 3077 8600 **F** +44 20 7430 1000

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

Duration: 06.06.2017 15:18:51 - 06.06.2017 15:19:21. This page 2 of 2 was completed at 06.06.2017 15:19:21

Received at the EPO on Jun 06, 2017 15:19:21. Page 2 of 2

J A • KEMP

BY FAX

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

EPO - Munich
11

07. Juni 2017

ATTENTION: CLAUDIA WEBER, LEGAL DIVISION

06 June 2017

Dear Ms Weber

Registration of J A Kemp as an association of professional representatives
- Association No. 811

J A Kemp has been registered as an association of professional representatives under the no. 811 with effect from 24 May 2017.

I request that all the live European cases on the EPO's records, in which the professional representative is an EP attorney from J A Kemp, be transferred to the newly registered association (J A Kemp - Association No. 811). A listing of the current members of the association was sent to me by the Legal and Unitary Patent Division by letter of 30 May 2017. If you need a copy of that letter please let me know.

I confirm that this is to include both pending European patent application and oppositions.

My understanding is that this transfer would normally trigger the issue of a hard copy EPO form on each affected case. We do not wish to receive an individual notification on each case affected. Please would you suppress the issue of those individual notification and instead simply send us one single listing of the cases affected.

We currently receive Communications on our EP cases via the EPO's Mailbox service. We wish this to continue.

Yours faithfully

~~Electronically Signed~~
NIGEL PRICE
J A KEMP



7.6.17.

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7430 1000
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



Application No.: 17168808.8

The search has started on 09.06.17 (see Notice from the European Patent Office dated 03/2013, OJ EPO 2013, 153).

Receiving Section



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
12.06.17

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1466
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Communication of amended entries concerning the representative (R. 143(1)(h) EPC)

As requested, for the above-mentioned European patent application / European patent the entries concerning the representative have been amended as follows:

J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
GB

The amendment will be recorded in the Register of European Patents.

Receiving Section



TITLE: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

APPLICANT: Regeneron Pharmaceuticals, Inc.

IPC CLASSIFICATION: A61K38/18, A61P27/00

EXAMINER: Rodrigo-Simón, Ana

CONSULTED DATABASES: NPL, MEDLINE, EPODOC, INET

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61K38/18G1

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

VEGF antagonist comprises VEGFR1 R2-FcAC1 (a) encoded by the nucleic acid sequence of SEQ ID NO:1 for use in treating age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose

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

1
EPO FORM 1503 03.02 (P04C01)

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

1
EPO FORM 1503 03.82 (P04C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	DO DV ET AL.: "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema.", BR J OPHTHALMOL, vol. 93, no. 2, February 2009 (2009-02), pages 144-1449, XP009158490, * abstract * * page 149, paragraph 2 * -----	3,5,6	
X	ANANT PAI ET AL.: "Current concepts in intravitreal drug therapy for diabetic retinopathy", SAUDI JOURNAL OF OPHTHALMOLOGY, vol. 24, no. 4, 30 June 2010 (2010-06-30), pages 143-149, XP002674122, * page 147, paragraph 4 * -----	3	
X	Regeneron Pharmaceuticals, Bayer, New York University: "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting", Evaluate.com 28 September 2008 (2008-09-28), XP002770952, Retrieved from the Internet: URL:http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=165320 [retrieved on 2017-06-09] * the whole document * ----- -/--	3,5,6	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (IPC)
Place of search Munich		Date of completion of the search 12 June 2017	Examiner Rodrigo-Simón, Ana
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

1
EPO FORM 1503 03.82 (P04C01)

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

1
EPO FORM 1503 03.02 (P04C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	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 * the whole document *	5	
T	STEWART MW.: "The expanding role of vascular endothelial growth factor inhibitors in ophthalmology", MAYO CLIN PROC, vol. 87, no. 1, January 2012 (2012-01), pages 77-88, XP002674124, * the whole document *		
L	WO 2012/097019 A1 (REGENERON PHARMA [US]; YANCOPOULOS GEORGE D [US]) 19 July 2012 (2012-07-19)	1-16	TECHNICAL FIELDS SEARCHED (IPC)
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 12 June 2017	Examiner Rodrigo-Simón, Ana
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

1
EPO FORM 1503 03.82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 17 16 8808

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-06-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0075319	A1	14-12-2000	AT 293164 T 15-04-2005
			AT 417928 T 15-01-2009
			AU 779303 B2 13-01-2005
			AU 2005201365 A1 28-04-2005
			BR 0011407 A 02-04-2002
			CA 2376379 A1 14-12-2000
			CN 1369009 A 11-09-2002
			CN 101433715 A 20-05-2009
			CN 103349781 A 16-10-2013
			CY 1108883 T1 02-07-2014
			CZ 303656 B6 30-01-2013
			CZ 20014387 A3 16-10-2002
			DE 60019415 D1 19-05-2005
			DE 60019415 T2 09-03-2006
			DK 1183353 T3 08-08-2005
			DK 1544299 T3 23-03-2009
			EP 1183353 A1 06-03-2002
			EP 1544299 A1 22-06-2005
			ES 2237429 T3 01-08-2005
			ES 2319305 T3 06-05-2009
			HK 1043388 A1 10-06-2005
			HK 1132653 A1 13-09-2013
			HK 1185798 A1 27-11-2015
			HR P20010908 A2 30-04-2005
			HU 230159 B1 28-09-2015
			HU 0201515 A2 28-08-2002
			HU S1300052 I1 29-08-2016
			IL 146890 A 08-07-2008
			JP 4723140 B2 13-07-2011
			JP 5273746 B2 28-08-2013
			JP 2003501089 A 14-01-2003
			JP 2011024595 A 10-02-2011
			LU 92195 I2 15-07-2013
			ME P3208 A 10-02-2010
			MX PA01012630 A 22-07-2002
			NO 332559 B1 29-10-2012
			NO 2013010 I1 17-06-2013
			NO 20016036 A 08-02-2002
			NZ 515913 A 30-01-2004
			PL 352246 A1 11-08-2003
			PT 1183353 E 30-06-2005
			PT 1544299 E 18-03-2009
			SK 17522001 A3 01-04-2003
			WO 0075319 A1 14-12-2000
			YU 86901 A 12-05-2004
			ZA 200110068 B 06-12-2002

EPO FORM P459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

page 1 of 3

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 145

Samsung Bioepis Exhibit 1067, pg. 145

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 17 16 8808

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-06-2017

Patent document cited in search report		Publication date	Patent family member(s)			Publication date

US 2006058234	A1	16-03-2006	NONE			

US 2005260203	A1	24-11-2005	US	2005260203	A1	24-11-2005
			US	2006030529	A1	09-02-2006
			US	2008220004	A1	11-09-2008

US 2007190058	A1	16-08-2007	AU	2005299701	A1	04-05-2006
			CA	2584305	A1	04-05-2006
			DK	1802334	T3	15-10-2012
			EP	1802334	A1	04-07-2007
			EP	2311433	A2	20-04-2011
			EP	2319492	A2	11-05-2011
			EP	2324848	A2	25-05-2011
			ES	2390676	T3	15-11-2012
			HK	1102106	A1	21-12-2012
			HR	P20120902	T1	31-12-2012
			NZ	590132	A	30-03-2012
			NZ	596663	A	26-07-2013
			NZ	598502	A	26-07-2013
			PT	1802334	E	28-11-2012
			RS	52539	B	30-04-2013
			SI	1802334	T1	31-12-2012
			US	2007190058	A1	16-08-2007
			US	2014086934	A1	27-03-2014
			WO	2006047325	A1	04-05-2006

US 2006172944	A1	03-08-2006	AU	2006214658	A1	24-08-2006
			CA	2621047	A1	24-08-2006
			EP	1877438	A2	16-01-2008
			US	2006172944	A1	03-08-2006
			US	2008085276	A1	10-04-2008
			WO	2006088650	A2	24-08-2006

WO 2012097019	A1	19-07-2012	AU	2012205599	A1	18-07-2013
			AU	2017200290	A1	02-02-2017
			CA	2824422	A1	19-07-2012
			CN	103533950	A	22-01-2014
			EP	2663325	A1	20-11-2013
			JP	2014503555	A	13-02-2014
			JP	2017061467	A	30-03-2017
			KR	20140043313	A	09-04-2014
			NZ	612593	A	27-03-2015
			SG	191334	A1	30-08-2013
			SG	10201509193U	A	30-12-2015
			US	2013295094	A1	07-11-2013

EPO FORM P459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

page 2 of 3

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 146

Samsung Bioepis Exhibit 1067, pg. 146

EP 17 16 8808

12-06-2017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2016101152 A1	14-04-2016
		WO 2012097019 A1	19-07-2012

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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

Description, Pages

1-22 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/1 as originally filed

2 The claimed compound, VEGF Trap-Eye, was also known as EYLEA, Aflibercept, VEGFR1R2-Fc[Delta]C1 (a), Zaltrap, AVE-0005, BAY-86-5321, NSC-724770, VEG Trap(R1R2) and VEGF Trap.

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

D1: XP002770953
D2: XP002770954
D3: XP002770951
D4: WO0075319
D5: US2006058234
D6: US2005260203
D7: XP26732998
D8: XP009158490
D9: XP002674122
D10: XP002770952
D11: US2007190058
D12: XP002674125
D13: US2006172944
D14: XP055328439

D15: XP009192770

D16: XP002674124

D17: WO2012097019 (parent application)

D1, D2 and D3 D3 are below described.

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-Trap-Eye for the treatment of diabetic retinopathy (P.147, §4).

D10 (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 docs).

D11 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).

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 describes the use of VEGFR1R2-Fc [Delta]C1(a) for the treatment of eye injuries by reducing angiogenesis (§8,§17 and claims 1-2). In the examples, a successful effect was shown in the treatment injury in mice.

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).

D16 (T-doc) reviews the known VEGF inhibitors used in ophthalmology.

4 **NOVELTY (Art. 54 (2) EPC):**

Claims 1, 2, 4 and 7-13 are not novel in the sense of Art. 54(2) EPC because:

D1 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 treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

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 D1 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 D1.

4.1 Claims 1, 2 and 7-13 are not novel in view of D1.

D2 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).

D2 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)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

4.2 Claims 1, 4 and 7-13 are not novel in view of D2.

D3 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). The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

4.3 **Claims 1, 4 and 7-13 are not novel in view of D3.**

4.4 **Claims 3, 5 and 6 are novel in the sense of Art. 54 (2) EPC because the specific therapeutic uses of the claimed compound have not been found to be disclosed in the prior art at hand, i.e 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.**

5 **INVENTIVE STEP (Art. 56 EPC):**

Claims 3, 5 and 6 are not inventive in the sense of Art. 56 EPC because:

- 5.1 **The closest prior art, D1**, describes the successful therapeutic use of the compound and dosage regime as claimed for the treatment of wet age-related macular degeneration.
- 5.2 **The difference** between D1 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.
- 5.3 **The problem to be solved** is seen in the provision of alternative therapeutic uses of the claimed compound and dosage regime.
- 5.4 **In support of an inventive step** the applicant provided Examples 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.
- 5.5 The attention of the applicant is drawn to the fact that the claimed diseases have a different nature and etiology than age-related macular degeneration.

It is therefore to be noted that, from the provided evidence, it cannot be concluded that diabetic retinopathy, central retinal vein occlusion or corneal neovascularization patients would necessarily 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 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*" 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 D1.

- 5.6 The same problem-solution approach would apply taking any of D2, D3, D4, D7, D8, D10, D11, 12, and D13 as closest prior art.
- 5.7 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.

- 5.8 **The subject-matter of claims 3, 5 and 6 is therefore not in accordance with the requirements of Art. 56 EPC.**

6 **SUFFICIENCY OF DISCLOSURE OF A THERAPEUTIC USE (Art. 83 EPC):**

Notwithstanding the above Art 56 EPC objections, claims 3 and 5-6 additionally contravene the requirements of Art. 83 EPC.

When a therapeutic use of a compound is claimed, the therapeutic effect is a technical feature of the claim. Sufficiency of disclosure of a further medical use claim requires that the therapeutic effect is either plausible or demonstrated at the filing date.

This is not the case of claims 3 and 5-6 which rely on technical effects (i.e. treatment of diabetic retinopathy, corneal neovascularization or central retinal vein occlusion) which are neither demonstrated nor plausible for the reasons given in point 5.4-5.6.



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
27.06.17

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1466
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

The following have been approved:

☒ Abstract ☒ Title

☐ The Abstract was modified and the definitive text is attached to this communication.

The following figure(s) will be published together with the abstract:

Refund of search fee

If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued once the date of publication of the European search report has been mentioned in the European Patent Bulletin (R. 69(1), R. 70(2) EPC).





European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
30.08.17

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1466 / 3222285
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

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

You are hereby informed that the technical preparations for the publication of the above-mentioned European patent application have been completed.

The application will be published on 27.09.17 with the European search report.

The publication number is: 3222285.

The publication will be mentioned in European Patent Bulletin number 2017/39.

(<http://bulletin.european-patent-office.org>).

Provisional protection under Article 67(1) and (2) EPC in the individual contracting states becomes effective when the conditions referred to in Article 67(3) EPC have been fulfilled. Provisional protection in the individual extension and validation states is governed by the national laws of the countries concerned. For more details, see Chapter III of the EPO brochure "National Law relating to the EPC" (www.epo.org/law-practice/legal-texts/national-law.html), which also contains information about the extension and validation system. Further information can also be found in the Official Journal of the European Patent Office.

The title of the invention in the three official languages of the European Patent Office is worded as follows:

VERWENDUNG EINES VEGF-ANTAGONISTEN ZUR BEHANDLUNG ANGIOGENER
AUGENERKRANKUNGEN
USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
UTILISATION D'UN ANTAGONISTE DU VEGF POUR TRAITER DES TROUBLES OCULAIRES
ANGIOGÉNIQUES

In all future communications to the EPO, please quote the application number as indicated above, i.e. including the final four figures (which identify the Directorate responsible for the subsequent procedure).

Remark

The publication can be downloaded, free of charge, from the EPO publication server <https://data.epo.org/publication-server/> or can be ordered from the Vienna sub-office upon payment of a fee (see Decision of the President of the EPO dated 12 July 2007 concerning the form of publication of European patent applications, European search reports and European patent specifications, Special edition No. 3, OJ EPO 2007, 97).

Note concerning renewal fees

Under Article 86 EPC renewal fees shall be paid to the EPO for the European patent application. These fees shall be due in respect of the third and each subsequent year, calculated from the date of filing. Due account should be taken that the EPO will not send invoices or reminders to pay any fees in due time.

Accelerated prosecution of European patent applications

Applicants wishing to accelerate proceedings before the EPO may file a request according to the programme for accelerated prosecution of European patent applications - "PACE" (OJ EPO 2010, 352). EPO Form 1005 is available on the EPO website (www.epo.org) for this purpose.

Receiving Section



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
02.10.17

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1466 / 3222285
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Communication pursuant to Rule 69 EPC - reminder concerning payment of the designation fee (Art. 79(2) EPC) and of the examination fee (Art. 94(1) EPC) - and invitation pursuant to Rule 70a(1) EPC

The date on which the European Patent Bulletin mentions the publication of the European search report for the above-mentioned European patent application is: 27.09.17.

Your attention is drawn to Article 79(2) and Rule 39(1) EPC as well as Article 94(1), Rule 70(1) and Rule 70a(1) EPC, according to which within **six months** of the above-mentioned publication date of the search report

- the designation fee must be paid,
- the request for examination must be filed and the examination fee must be paid,
- comments on the objections raised in the opinion accompanying the European search report and/or any amendments to the description, claims and drawings correcting any deficiencies noted in the opinion must be filed (R. 70a(1), 137(2) EPC; Guidelines for Examination in the EPO, B-XI, 8).

1. Payment of the designation fee and of the examination fee

The current designation fee for one or more Contracting States designated is: EUR 585,00

The current examination fee is: EUR 1635,00

If the written request for examination is filed in an admissible non-EPO language in accordance with Article 14(4) EPC, a reduction of the examination fee according to Rule 6(3) EPC applies.

For European patent applications filed on or after 01.04.2014, the reduction applies only if the applicant(s) has (have) declared to be an entity or a natural person within the meaning of Rule 6(4) EPC (Decision of the Administrative Council of 13 December 2013, OJ EPO 2014, A4).

If the designation fee and the examination fee are not paid within the period laid down in Rule 39(1) and Rule 70(1) EPC, the application **will be deemed to be withdrawn** (R. 39(2) and Art. 94(2) EPC).

Any extension or validation fees are also payable within the above-mentioned period.

2. Comments on the opinion accompanying the European search report and filing of amendments

Should the reply to the invitation pursuant to Rule 70a(1) EPC be filed in an admissible non-EPO language, a translation is to be submitted within one month of its filing (R. 6(2) 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).

Should you not comply with this invitation within the time limit, the application **will be deemed to be withdrawn** in accordance with Rule 70a(3) EPC.

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the examination fee and the designation fee will be debited on the last day of the period for payment. For further details see the Arrangements for the automatic debiting procedure, supplementary publication 3 - OJ EPO 2015.

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.

Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

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

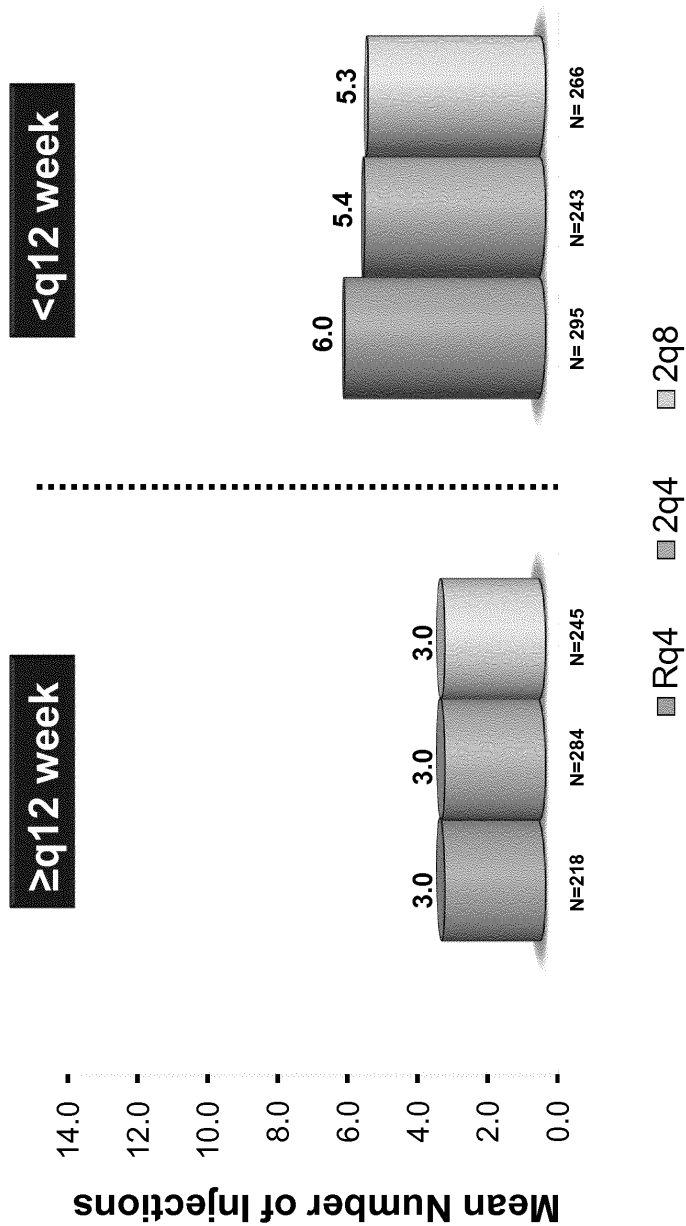
Note concerning renewal fees

Under Article 86 EPC renewal fees shall be paid to the EPO for the European patent application. These fees shall be due in respect of the third and each subsequent year, calculated from the date of filing. Due account should be taken that the EPO will not send invoices or reminders to pay any fees in due time.

Receiving Section

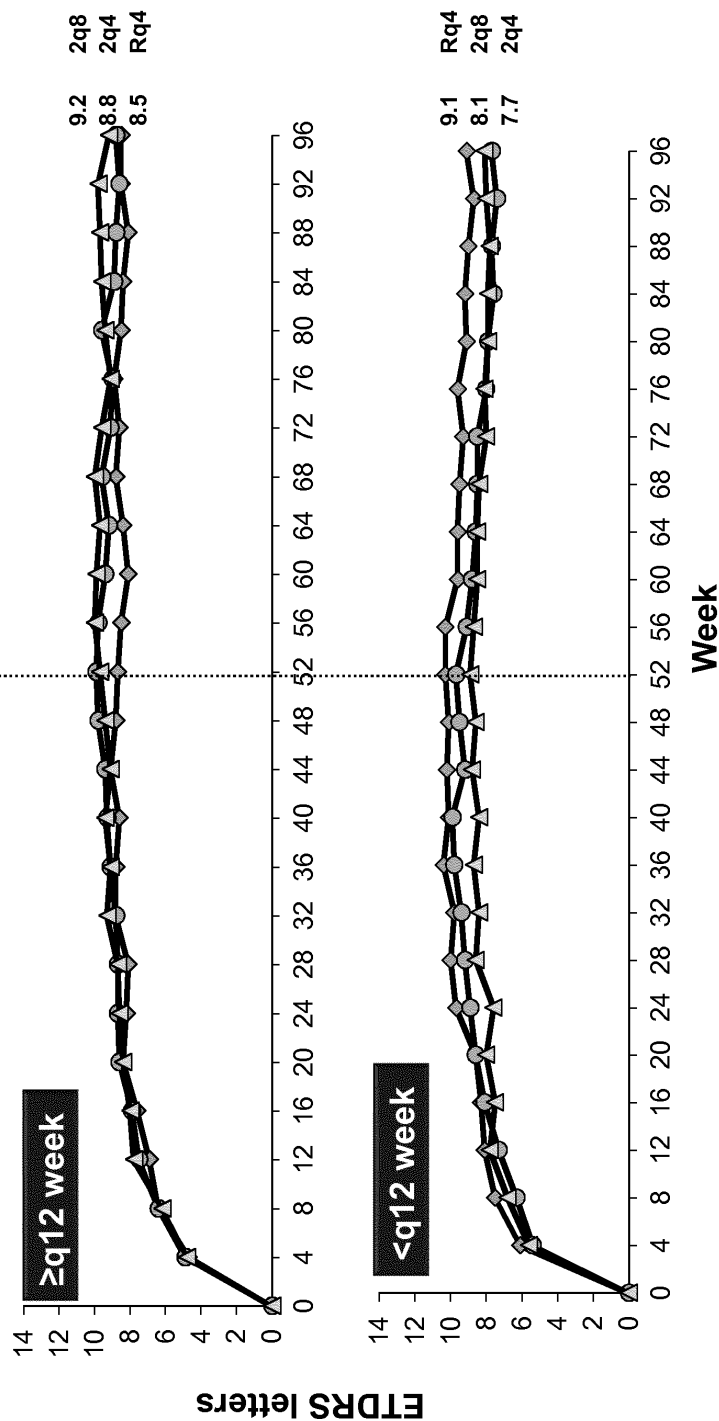


Mean Number of Injections Weeks 52–96



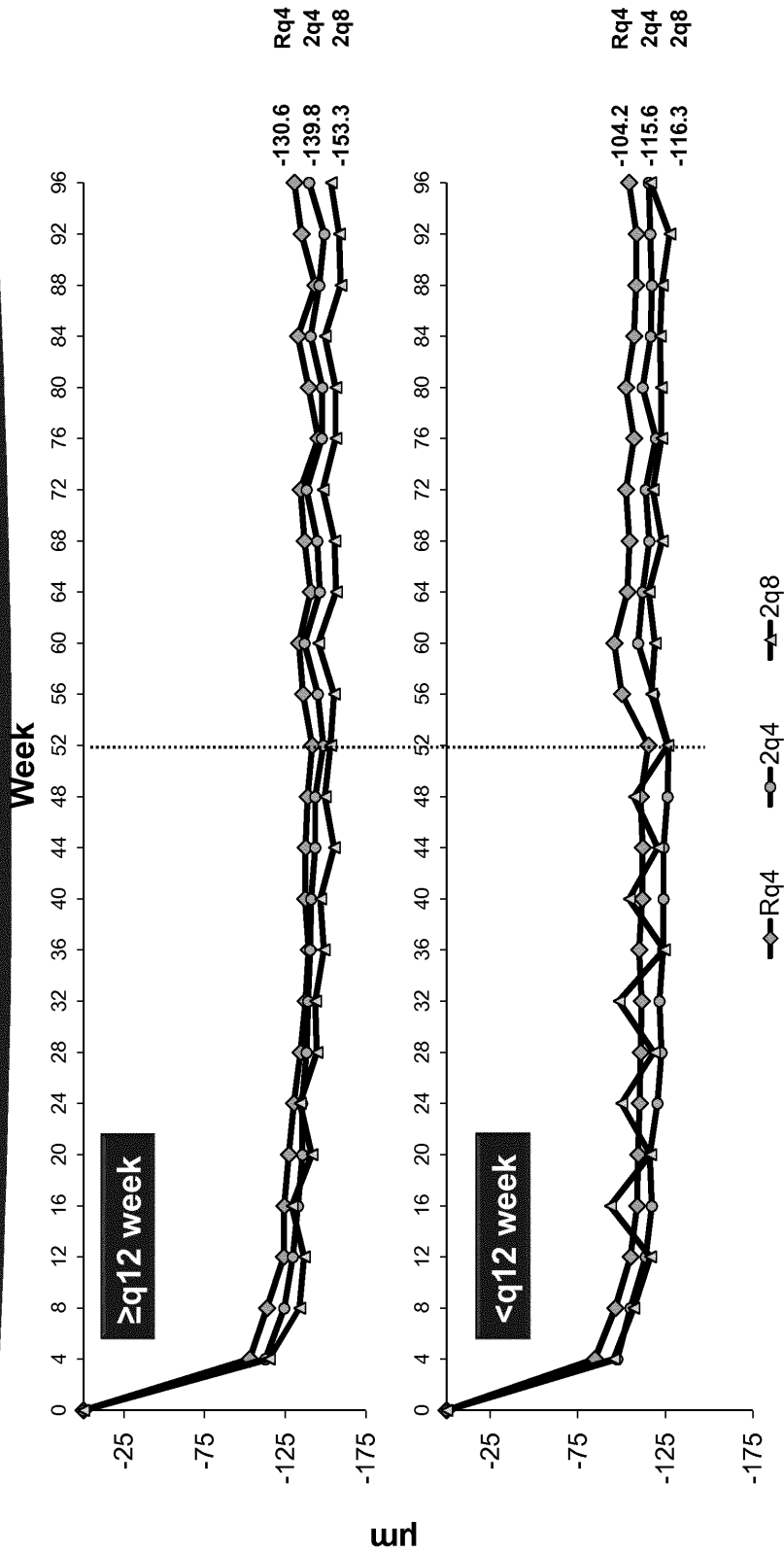
FAS, Year 2 medication completers. A minimum of at least 3 injections required with mandatory quarterly dosing

Mean Change in Best-Corrected Visual Acuity from Baseline Through Week 96



FAS, LOCF, Year 2 medication completers. ≥ q12 week Rq4 n= 218, 2q4 n= 284, 0.5q4 n=217, and 2q8 n=245. <12q Week Rq4 n=295, 2q4 n=243, 0.5 q4 n=282, and 2q8 n=266

Mean Change in Central Retinal Thickness from Baseline Through Week 96



FAS, LOCF, Year 2 medication completer, ≥ q12 week Rq4 n= 218, 2q4 n= 284, 0.5q4 n=217, and 2q8 n=245. <12q Week Rq4 n=295, 2q4 n=243, 0.5 q4 n=282, and 2q8 n=266

If you are having problems viewing this email, please use the following address:
<http://www.visioncareprofessional.com/emails/amdupdate/index.asp?issue=42>

presented by
Ophthalmology
 MANAGEMENT

AMD Update

June 2010, Issue 42

The "Treat and Extend" Dosing Regimen of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration

Michael Engelbert, MD
 K. Bailey Freund, MD
 Edward S. Harkness Eye Institute, Columbia University College of Physicians & Surgeons, New York, NY,
 Vitreous-Retina-Macula Consultants of New York, New York, NY
 LuEsther T. Mertz Retinal Research Center, New York, NY
 This work is supported by The Macula Foundation, Inc..



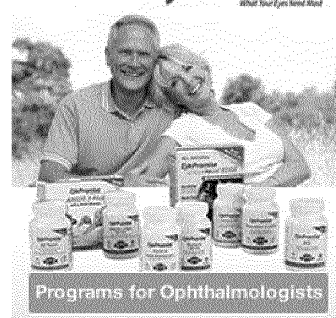
While monthly injections of intravitreal anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (AMD) have produced visual outcomes superior to prior therapies,^{1,2} the frequency of office visits and injections can place a tremendous burden on patients and the health care system. Unfortunately, the PIER trial,³ which is the only randomized, double-blind, sham-controlled trial investigating a less frequent dosing regimen, yielded inferior visual outcomes compared to outcomes reported after monthly dosing. Patients in the PIER trial were examined and treated quarterly following an initial series of three monthly injections. The open-label, non-randomized PrONTO study also employed three initial monthly injections but was followed by "as needed" dosing based on changes in visual acuity, clinical findings and optical coherence tomography (OCT) evaluation.^{4,5} The PrONTO regimen appeared to achieve visual results similar to monthly dosing with fewer injections, but patients still required monthly visits, examinations, and OCTs. Furthermore, after the initial mandated series of three injections, this protocol allowed fluid to re-accumulate at the fovea before treatment was repeated, raising concerns regarding incremental long-term vision loss and the possibility of new hemorrhages during periods without VEGF inhibition.^{6,7,8}

The "Treat and Extend" dosing regimen is a tailored maintenance regimen intended to achieve optimal visual results with two additional goals.⁹ Like PIER and PrONTO, it consists of at least three initial monthly injections, but, once stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved, patients continue to receive regular maintenance injections at increasing intervals. Once stability is achieved with monthly dosing, the patient is instructed to return in six weeks. Visual acuity, clinical findings, and OCT changes are recorded again and patients receive an injection regardless of the presence or absence of disease activity. However, the interval to the next visit (and scheduled injection) is based on an observed change in the above parameters. If there are no changes, the interval to the next visit is extended to seven or eight weeks (hence the term "Treat and Extend"). However, if there is evidence of renewed disease activity, the interval for the next scheduled injection and examination is shortened. In our own clinical practice, we rarely extend the interval between injections and examination beyond 8-9 weeks.

One goal of "Treat and Extend" is to reduce the treatment burden by reducing number of patient visits and the number of imaging studies performed by eliminating the need for the monthly visits necessitated by alternative dosing strategies. We recently reported success in achieving this goal in two small cohorts of eyes with newly diagnosed type 1 (occult)¹⁰ and type 3 (retinal angiomatous proliferation)¹¹ neovascularization. In these reports, the eyes with type 3 vessels had a sustained visual improvement of approximately 2 Snellen

What Your Eyes Need Most.

EyePromise
 What Your Eyes Need Most



Ingrid U. Scott, MD, MPH, Editor



Professor of Ophthalmology and
 Public Health Sciences,
 Penn State College of Medicine

PRINT FRIENDLY VERSION

FORWARD TO COLLEAGUE

NEWSLETTER ARCHIVE

AMD UPDATE WEBSITE

lines while the eyes with type 1 vessels achieved visual stabilization. The number of office visits and injections was reduced by 25-50% compared to a monthly dosing regimen.

A second goal of the "Treat and Extend" dosing regimen is to reduce the risk of new sight-threatening submacular hemorrhages. We recently demonstrated a statistically significant increase in macular hemorrhages when patients in the PIER trial were switched from a monthly to quarterly dosing regimen.⁶ Unfortunately, large and potentially devastating submacular hemorrhages may occur almost immediately after a high-quality OCT examination showing an absence of fluid.^{7,8} Theoretically, eyes treated with an OCT-guided "as needed" regimen, in which patients may go long intervals without VEGF suppression, could be at a greater risk for sight-threatening submacular hemorrhages compared to eyes receiving more frequent and regular anti-VEGF treatments. In our two retrospective series, we did not observe any sight-threatening macular hemorrhages. Also, unlike the ANCHOR, MARINA and PrONTO studies which are limited to 24 months of follow-up, 17 of our 28 patients completed 36 month follow-up. We are not aware of any other dosing regimen of anti-VEGF therapy that has demonstrated stable or improved VA out to three years.

While initial results of the "Treat and Extend" dosing regimen appear promising, the strategy requires further validation in a larger randomized trial. Clinicians should view the current data regarding different regimens critically when deciding which dosing strategy is best for individual patients.

REFERENCES

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1419-31
2. Brown DM, Kaiser PM, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1432-1444
3. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. Feb 2008;145(2):239-248.
4. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. Apr 2007;143(4):566-583.
5. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol* 2009 Jul;148(1):43-58.e1. Epub 2009 Apr 18.
6. Barbazetto I, Saroj N, Freund KB. Dosing regimen and the frequency of macular hemorrhages in neovascular age-related macular degeneration treated with ranibizumab. Presented at the Annual Meeting of the Retina Society, September 2008.
7. Margolis R, Freund KB. Hemorrhagic recurrence of neovascular age-related macular degeneration not predicted by spectral domain optical coherence tomography. *Retinal Cases and Brief Reports*, in press.
8. Levine JP, Marcus I, Sorenson JA, Spaide RF, Cooney MJ, Freund KB. Macular hemorrhage in neovascular age-related macular degeneration after stabilization with antiangiogenic therapy. *Retina*. 2009 Sep;29(8):1074-9.
9. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. *Am J Ophthalmol*. 2007 Apr;143(4):679-80.
10. Engelbert M, Zweifel SA, Freund KB. Long-term Follow-up for Type 1 (sub-RPE) Neovascularization using a "Treat and Extend" Dosing Regimen of Intravitreal Anti-vascular Endothelial Growth Factor Therapy". *Retina*, accepted for publication.
11. Engelbert M, Zweifel SA, Freund KB. "Treat and extend" dosing of intravitreal anti-vascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. *Retina*. 2009 Nov-Dec;29(10):1424-31.

Erratum

We apologize that last month's article, *Comparison of Two Doses of Intravitreal Bevacizumab as Primary Treatment for Subfoveal CNV Associated with AMD at 24 Months: The Pan-American Collaborative Retina Study Group* by J. Fernando Arevalo, MD, FACS and Martin A. Serrano, MD was originally scheduled for a later issue but was in error released in May 2010.

THE VIEWS EXPRESSED IN AMD UPDATE DO NOT NECESSARILY REFLECT THOSE OF THE SPONSOR.

If you prefer not to receive e-mail from us, please use the following link to remove your e-mail address from our list: [Unsubscribe](#)

This message was transmitted by [PentaVision LLC](#) | 321 Norristown Road, Suite 150, Ambler, PA 19002 | 215-628-6550

[View the PentaVision LLC Privacy Policy](#) | [Contact Us](#) - Please do not reply to this e-mail message.

Please make sure our e-mail messages don't get marked as spam by adding visioncareprofessionalemail.com to your "approved senders" list.



Letter accompanying subsequently filed items

Representative:

J A Kemp
811
14 South Square
Gray's Inn
London Greater London WC1R 5JJ
United Kingdom

Phone: +44 20 3077 8600
Fax: +44 20 7430 1000
E-mail: mail@jakemp.com

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

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

Application number

17168808.8

Applicant's or representative's reference

N400458EP-A

	Description of document	Original file name	Assigned file name
1	Document filed during examination procedure	Engelbert_et_al_2010 N400458EP-A AXB.pdf	EXAM-1.pdf
2	Document filed during examination procedure	12 Week data N400458EP-A AXB.pdf	EXAM-2.pdf
3	Document filed during examination procedure	Mean Number of Injections Weeks 52-96 N400458EP-A AXB.pdf	EXAM-3.pdf
4	Document filed during examination procedure	Mean Change Best-Corrected Visual Acuity Wk96 N400458EP-A.pdf	EXAM-4.pdf
5	Amended claims (clean copy)	Amended claims (clean) Mar18 N400458EP-A AXB.PDF	CLMS-1.PDF
6	Amended claims with annotations	Amended claims (tracked) Mar18 N400458EP-A AXB.pdf	CLMS-HWA-1.pdf
7	Request for examination	Response to SO N400458EP-A AXB.PDF	EXAMREQ-1.PDF

	Fees	Factor 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	585.00	585.00
15-2	006 Examination fee - For applications filed on/after 01.07.2005	1	1 635.00	1 635.00
	Total:		EUR	2 220.00

	Payment	
1	Method 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.	

N400458EP-A

	Deposit account number:	28050038
	Account holder:	J A Kemp
2	Refund/Reimbursement	
	Reimbursement (if any) to be made to EPO deposit account:	28050038
	Account holder:	J A Kemp

Signatures

Place:
Date: 26 March 2018
Signed by: Andrew Bentham 23464
Association: J A Kemp
Representative name: Andrew BENTHAM
Capacity: (Representative)

N400458EP-A

J A • K E M P

BY ONLINE FILING

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

26 March 2018

Dear Sirs

European Patent Application No. 17168808.8
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP-A AXB

I request substantive examination of this application. I request that the following fees are deducted from deposit account 2805.0038 in the name of J A Kemp:

- fee for substantive examination (1635 EUR); and
- a single combined designation fee (585 EUR) for all available countries i.e. 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, and TR.

A debit voucher for these fee payments is included with the online filing form. Please deduct any underpayment of these fees from deposit account 2805.0038. Please credit any overpayment of these fees to deposit account 2805.0038.

Please amend the present application by replacing the claims at present on file with the new claims attached.

In order to assist the Division in assessing the amendments being made, please also find attached a copy of the previous claims showing the changes tracked-in is also attached.

The following documents referred to below are also attached:

- a Summary of additional clinical trial results from the Applicant “*12 Week Data*”;
- a slide showing “*Mean Number of Injections Weeks 52-96*” in the further trials performed;

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • PARIS • MUNICH
14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7430 1000
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

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 167

- a slide showing “*Mean Change in Best-Corrected Visual Acuity from Baseline Through Week 96*”; and
- Engelbert *et al* (2010) - AMD Update.

Amendments & Basis

Purely in order to facilitate prosecution, and not indicating agreement with objections raised, a number of amendments are now being made to the claims. The amendments can be summarised as follows:

- Claim 1 has been amended to recite that the first five tertiary doses are administered eight weeks after the immediately preceding dose. Basis for the amendment is given at, for instance, paragraph [0043] of the application as filed which refers to the first five tertiary doses being given at such intervals.
- New claim 14 finds basis in the application as filed in “*Further Numbered Embodiments of the Invention*” 21, 25 and 26 at page 21, as well as in paragraphs [0009], [0017], and [0061] and Example 4.
- New claim 15 finds basis in the application as filed in “*Further Numbered Embodiments of the Invention*” 21, 24 and 26 at page 21, as well as in paragraph [0019].
- New claim 16 finds basis in the application as filed in “*Further Numbered Embodiments of the Invention*” 21, 25 and 26 at page 21, as well as in paragraph [0017].
- New claim 17 finds basis in the application as filed at page 21, as well as in paragraph [0050].

The above amendments find also basis in the same locations in the parent application, apart from the “*Further Numbered Embodiments of the Invention*” cited above, which are present as the equivalently numbered original claims of the parent.

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

Please also note that the Applicant reserves the right to file divisional application(s), including to pursue subject matter now being excised from the claims.

Novelty - Article 54 EPC - Item 4 of the Opinion

The amended claims are focussed on the feature of doses of the recited VEGF antagonist being administered, where at least some of the doses are administered twelve weeks after the immediately preceding dose.

None of D1 to D17, including D1 to D3 on which objections were raised, disclose the specific regimens now recited by the claims and in particular the administration of the tertiary doses at intervals of twelve weeks. For instance, D1 does not disclose such tertiary dosing. D1 specifies PRN dosing which is limited such that dosing

typically occurs monthly and in no case involves tertiary dosing at intervals of twelve weeks. The passage at page 2, third full paragraph cited in the Search Opinion does not comprise such dosing, nor any other portion of the document either. The same is the case for both D2 and D3 which each lack any disclosure of tertiary dosing at 12 week intervals. Indeed, many of the references to “12 weeks” within the documents are also indications that the dosing is being carried out every 4 weeks for 12 weeks. That is not, of course, “12 week dosing” as claimed.

As such, the subject matter of the amended claims is novel over the cited prior art as a whole, including over D1 to D3 which the specific objections raised are based on.

Inventive Step - Article 56 EPC - Item 5 of the Opinion

(a) The claimed invention and its advantages

Prior to addressing the specific objections raised, it may be helpful to discuss the claimed invention and the advantages it displays. As discussed above, the amended claims revolve around a particular dosing regimen approach including dosing which involves administration of at least some of the doses of the VEGF antagonist, particularly the tertiary doses, at twelve week intervals. The identification by the present application as filed of employing longer intervals between doses in a dosing regimen for the recited eye disorders with the stated VEGF antagonist represents a significant advance.

Treatment for eye disorders such age-related macular degeneration (AMD) using the recited VEGF antagonist requires injection into the eye of the patient. This treatment protocol is expensive, painful to the patient, inconvenient for the patient as well as the patient’s family, psychologically and physically traumatic, and subjects the patient to potential adverse effects such as infection at each treatment event. Accordingly, any treatment protocol which can reduce the frequency of treatments would be considered very advantageous. However, prior to the present application, such longer dosing intervals were not considered.

For instance, the attached Engelbert *et al* includes statements indicating that the conventional wisdom in the art was quite sceptical with respect to successfully treating patients using less frequent dosing, and unsuccessful in such treatment. In particular, please see the first paragraph of Engelbert *et al* discussing the issues with the burden placed on patients through regular intra-ocular injections and the second paragraph indicating that intervals between dosing were not extended to the much longer 12 week intervals now recited by the claims. Hence, the reality was there was effectively a prejudice in the art against longer dosing intervals. Thus, the presently claimed approach which utilizes 12 week dosing is counter to conventional wisdom.

The present application as filed identifies as a preferred approach such tertiary dosing involving some of the doses being given at 12 week intervals. By way of further illustration of the claimed approach, please see the additional experimental data now filed corroborating further what is set out in the application as filed and illustrating the advantages of the approach. For instance, please see the attached summaries of the additional clinical data obtained titled “12 Week Data”, “Mean Number of Injections Weeks 52-96”, and “Mean Change in Best-Corrected Visual Acuity from Baseline Through Week 96”. Overall, those provide data showing that

the 12 week dosing that the present claims are based around can be carried out with at least as effective results as those obtained with more frequent dosing. A considerable number of patients did finish the trial with such 12 week dosing for the tertiary doses illustrating that, contrary to what is indicated in documents such as Engelbert *et al*, for a large proportion of patients 12 week dosing is a real and effective approach, with the benefit of reduced frequency of intra-ocular injection.

In identifying for the first time the approach of giving at least some of the doses at 12 week intervals represents one of the key contributions of the present application.

(b) The claimed approach is inventive over the cited art

The Search Opinion adopts a large number of documents as closest prior art, arguing that any of D1 to D14 may be adopted as such. As an illustrative example D1 may be adopted as such for the sake of argument, but the reasons for inventive step apply equally to all of the cited documents. As discussed above in relation to novelty, the focus of the regimens referred to in D1 is monthly dosing and there is no dosing at anything approach 12 week intervals. Starting from D1:

- The **technical problem to be solved** may be formulated as the provision of an improved regimen for particular eye disorders.
- The **solution to the technical problem** is provided by the specific regimens of the claims that revolve around dosing with 12 week intervals for some of the doses. That represents an improvement because, as explained above, it goes against the view-point in the art that shorter dosing intervals were important and helps reduce the burden on the patient of regular intra-ocular dosing.

The solution to the technical problem would not have been obvious from D1 or any of the other cited prior art documents, whether considered alone or in combination with each other. That is at least the case for the reasons that:

- Potentially, there are an infinite number of different treatment protocols which could be tested for a given drug because of variation in dosing intervals and so on. There is no pointer in any of the cited art documents to the specific regimen that the claims are based around which involve 12 week dosing.
- As illustrated by the attached, Engelbert *et al* it is not just that there was a lack of teaching of the specific regimen claimed, the art actively taught against employing longer dosing intervals as now recited by the claims. For instance, Engelbert *et al* second paragraph that it was not considered advisable to extend dosing beyond a certain point and that was well below the 12 week dosing interval that the present claims are based around. The art therefore included a prejudice against the claimed approach actively stopping the skilled person arriving at the solution to the technical problem.
- The application as filed identifies for the first time the approach of 12 week dosing. As corroborated further by the additional data now filed, it is illustrated that the application as filed makes a significant contribution in identifying 12 week dosing. The additional data illustrates the approach of tertiary dosing involving administration of the VEGF antagonist at a frequency

of up to once every 12 weeks, is surprisingly effective in the treatment of angiogenic eye disorders and is at least equivalent in efficacy as compared with the prior known more frequent dosing regimens. The fact that the claimed approach allows a large proportion of patients to have a regimen that, at least in part, comprises 12 week dosing and so less frequent intra-ocular injections is a significant contribution. Such unexpected advantages would not have been predictable from the art, particularly given the existence of documents such as Engelbert *et al.*

The solution to the technical problem would not therefore have been obvious to the skilled person. The subject matter of the amended claims is therefore inventive over the cited prior art as a whole.

Sufficiency - Item 6 of the Opinion

The Opinion refers in Item 6 to plausibility. What is though now claimed is plausibly disclosed in the application as filed and also the parent application. For instance, in the parent application as filed original claim 5 and 25, page 4, fourth from bottom line, Example 2 on page 9, and Example 4 in paragraph [0044] all give prominence to dosing at 12 week intervals, as do the equivalent portions of the present application as filed. Hence, the application as filed does identify the importance of 12 week dosing and plausibly disclose it. The post-filing data now provided also further corroborates the claimed approach and illustrates its advantages. The relevant case-law illustrates that such post-filing data may be taken into consideration.

The subject matter of the claims is therefore plausibly disclosed and is also enabled.

Conclusions

It is believed that the points raised in the Search Opinion have all been addressed. If any points remain outstanding the Examiner is welcome to telephone or issue a first Examination Report. Purely as a precaution, in the unlikely event that the Division consider refusing the application at any point, Oral Proceedings are requested.

Please note that the Applicant does not consent to amendments to the claims without their prior consultation. Hence, if the Division wish to propose amendments to the claims, the Examiner is asked to please telephone the undersigned so that the Applicant can be consulted.

Yours faithfully

Electronically Signed
A BENTHAM
ASSOCIATION NO. 811

CLAIMS - TRACKED

1. A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first ~~four~~ five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and

wherein the VEGF antagonist comprises 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 0.5 mg to 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

13. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

14. A VEGF antagonist for use in a method for treating wet age related macular degeneration in a patient, the method comprising sequentially administering to the patient a

single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

_____ wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

_____ wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and

_____ wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

15. A VEGF antagonist for use in a method for treating diabetic macular edema in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the administration of 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 at least 8 weeks after the immediately preceding dose; and

_____ wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

16. A VEGF antagonist for use in a method for treating central retinal vein occlusion in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the use of one or more tertiary doses of the VEGF antagonist;

_____ wherein each secondary dose is for administration 4 weeks after the immediately preceding dose;

_____ wherein each tertiary dose is for administration at least 12 weeks after the immediately preceding dose; and

_____ wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

17. The VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient of claim 1, wherein exclusion criteria for the patient to receive the VEGF antagonist include:

(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.

CLAIMS

1. A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and

wherein the VEGF antagonist comprises 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 0.5 mg to 2 mg of the VEGF antagonist.

12. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

13. The VEGF antagonist for use according to claim 11, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

14. A VEGF antagonist for use in a method for treating wet age related macular degeneration in a patient, the method comprising sequentially administering to the patient a

single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and

wherein the VEGF antagonist comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

15. A VEGF antagonist for use in a method for treating diabetic macular edema in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the administration of 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 at least 8 weeks after the immediately preceding dose; and

wherein the VEGF antagonist comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

16. A VEGF antagonist for use in a method for treating central retinal vein occlusion in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the use of one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is for administration 4 weeks after the immediately preceding dose;

wherein each tertiary dose is for administration at least 12 weeks after the immediately preceding dose; and

wherein the VEGF antagonist comprises VEGFR1R2-Fc Δ C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

17. The VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient of claim 1, wherein exclusion criteria for the patient to receive the VEGF antagonist include:

- (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.



Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	6177153	
Application number	EP17168808.8	
Date of receipt	26 March 2018	
Receiving Office	European Patent Office, The Hague	
Your reference	N400458EP-A	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (2 p.) EXAM-2.pdf\12 Week data N400458EP-A AXB.pdf (1 p.) EXAM-4.pdf\Mean Change Best- Corrected Visual Acuity Wk96 N400458EP-A.pdf (1 p.) CLMS-HWA-1.pdf\Amended claims (tracked) Mar18 N400458EP-A AXB.pdf (4 p.)	ep-sfd-request.xml EXAM-1.pdf\Engelbert_et_al_2010 N400458EP-A AXB.pdf (2 p.) EXAM-3.pdf\Mean Number of Injections Weeks 52-96 N400458EP-A AXB.pdf (1 p.) CLMS-1.PDF\Amended claims (clean) Mar18 N400458EP-A AXB.PDF (4 p.) EXAMREQ-1.PDF\Response to SO N400458EP-A AXB.PDF (5 p.)
Submitted by	CN=Andrew Bentham 23464	
Method of submission	Online	
Date and time receipt generated	26 March 2018, 18:31 (CEST)	
Message Digest	8D:0B:47:7D:C1:DB:57:FA:FA:4A:9E:BD:FF:29:73:6B:A1:43:9C:B1	

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/

ClinicalTrials.gov archive

A service of the U.S. National Institutes of Health

Developed by the National Library of Medicine

← 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 <u>Time Frame: week 52</u> 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

**Third Party Observation for application Number
EP20170168808**

Successful submission of observation took place on 12/06/2019
09:43

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Publication Number: EP3222285

Applicant: REGENERON PHARMA[US]

Date of publication: 27.09.2017

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

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2) November 30, 2010()

Uploaded documents:

1. NPL1_NPL1_Annex4.pdf

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:

Claims 1-16 are not inventive in view of D1

We fully agree with the European search opinion regarding what D1 has disclosed (see point 4.1 sheet 3 to 4).

Specifically, D1 discloses that 2 mg aflibercept dose intravitreal 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 (see second page, third paragraph).

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline of D1).

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-FcC1(a) to which claim 1 refers.

According to D1, 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 D1.

Novel features not known from the prior art:

The difference between D1 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No supportive evidence

No evidence provided by the present application demonstrates that patients with any one of the above-mentioned disorders will necessarily benefit from the dosage regimen specified in claim 1.

Specifically, Examples 1-4 direct to the treatment of wet age-related macular degeneration (wet AMD), wherein none of the dosage regimen in these Examples comprises “the first five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose” as specified in claim 1.

Example 5 directs to treatment of diabetic macular edema. Specifically, 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).

Example 6 directs to treatment of macular edema secondary to central retinal vein occlusion (CRVO). Specifically, naive patients with macular edema secondary to CRVO received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed (PRN dosing) from Week 24 through Week 52. Thus, the dosage regimen of the Example 6 is as follows: an initial dose at week 0 and four secondary doses at weeks 4, 8, 12, 16 and 20, and then tertiary doses as needed until week 52.

Therefore, no technical effect for the proposed VEGF antagonist and dosage regime in the treatment of AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization has been demonstrated in the present application.

Applicant provided further documents on 26 March 2018 to show that the 12 week dosing that the present claims are based around can be carried out with at least as effective results as those obtained with more frequent dosing. However, Engelbert et al is a post-published document relating to AMD, and other three slides fail to specify the disorder to be treated. Therefore, these post-

filed documents fail to demonstrate the therapeutic effect of the proposed VEGF antagonist towards AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization.

Besides, Engelbert et al is a post-published document, and no evidence shows that the other three slides are available to the skilled person before the effective date of the patent.

According to decision T 1329/04, the verification of whether or not the claimed solution actually solves the problem, i.e. whether the claimed subject-matter actually provides the desired effect, must be based on the data in the application. Post-published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved. (see Case Law of the Boards of Appeal, I. D. 4.6 Solving a technical problem - post-published documents)

Therefore, such four documents filed by applicant should not be considered.

The objective technical problem starting from D1 therefore may be reformulated as provision of alternative therapeutic use and provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FcCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT (see 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) all of which cited in European search opinion sheet 2 to sheet 3), and that adjusting dosing intervals to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D1.

Accordingly, claims 2-13 are not inventive in view of D1. For the similar reasons claims 14-16 are not inventive in view of D1.

5.2. Inventive step (2)

Features known from the prior art:

Claim 17 is not inventive in view of D1 and Annex 4 (NPL1)

Re disclosure of D1, see above.

Novel features not known from the prior art:

The difference between D1 and claim 17 further include three exclusion criteria.

The technical effect caused or technical problems solved by the novel features:

However, the fact that D1 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 D1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

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 (NPL1). 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 paragraph [0050] of the patent. Though claim 17 only select 3 exclusion criteria, 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, 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, claim 17 does not involve an inventive step.

5.3. Inventive step (3)

Features known from the prior art:

Claims 1-17 are not inventive in view of D2

We fully agree with the European search opinion regarding what D2 has disclosed (see point 4.2 sheet 4).

D2 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).

D2 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)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

Novel features not known from the prior art:

The difference between D2 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D2 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FeCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D2.

Accordingly, claims 2-13 are not inventive in view of D2. For the similar reasons claims 14-17 are not inventive in view of D2.

5.4. Inventive step (4)

Features known from the prior art:

Claims 1-17 are not inventive in view of D3

We fully agree with the European search opinion regarding what D3 has disclosed (see point 4.3 sheet 4 to 5).

D3 describes 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 or as needed dosing. Improvements in visual acuity compared to patients receiving laser therapy were reported (§4).

Novel features not known from the prior art:

The difference between D3 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D3 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FeCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D3.

Accordingly, claims 2-13 are not inventive in view of D3. For the similar reasons claims 14-17 are not inventive in view of D3.

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)

Re Claims 1 to 13:

Claim 1 has been amended to require that the first FIVE tertiary doses are administered 8 weeks after the immediately preceding dose.

However, claim 5 of the parent application does not directly and unambiguously disclose that amendment. It is apparent that claim 5 of the parent application only recites that the first FOUR tertiary doses, not the first five tertiary doses, are administered 8 weeks after the immediately preceding dose.

In his letter dated March 26, 2018, the applicant alleged that the basis for such amendment is given at paragraph [0043] of the application as filed which refers to the first five tertiary doses being given at such intervals.

However, paragraph [0043] in the present application or in the parent application does not directly and unambiguously disclose that amendment either.

Specifically, first, paragraph [0043] belongs to example 4, thus the condition is age-related macular degeneration, not other angiogenic eye disorder such as diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization. Besides, in paragraph [0043], only 2Q8 regimen seems to be a relevant basis. In 2Q8, 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks, i.e. an initial dose at week 0 and two secondary doses (!) at weeks 4 and 8, and then 5 tertiary doses (!!!) of 2 mg every eight weeks (!).

Accordingly, the application as filed or the parent application does not provide a basis for claims 2 to 13 and

Re Claim 17:

Claim 17 is a dependent claim of claim 1, which further requires that the patient which is selected for treatment does not exhibit the exclusion criteria (1) to (3).

Applicant alleges that basis can be found at least in paragraph [0050] and page 21.

However, neither paragraph [0050] nor page 21 provides basis for new added claim 17.

In fact, paragraph [0050] of the present or the parent application does not directly and unambiguously disclose that only one or some exclusion criteria is to be applied. Rather, it is apparent from the overall context of the example that ALL (!) exclusion criteria listed in this paragraph should be applied when selecting the patient for treatment.

In summary, the Claims 1-13 and 17 do not meet the requirements of Article 76(1) and Article 123(2) EPC.

6.2. Sufficiency of disclosure (Article 83 EPC)

We fully agree with the European search opinion regarding claims 3 and 5-6 additionally contravene the requirements of Art. 83 EPC.

For the same reason new added claim 16 (central retinal vein occlusion) contravenes the requirements of Art. 83 EPC.

Besides, notwithstanding the above Article 76(1), Article 123(2) EPC and Art 56 EPC objections towards claims 1 to 14, 16-17, said claims additionally contravene the requirements of Art. 83 EPC.

When a therapeutic use of a compound is claimed, the therapeutic effect is a technical feature of the claim. Sufficiency of disclosure of a regimen claim requires that the therapeutic effect is either plausible or demonstrated at the filing date.

As discussed above, no therapeutic effect is demonstrated at the filing date. Since the dosing interval extends from 8 weeks to 12 weeks, without further evidence, the skilled person cannot reasonably expect from examples recited in the present specification that such extended interval may have therapeutic effects.

Applicant alleged in “sufficiency” section of his letter dated March 26, 2018 that evidence supporting the plausibility of the therapeutic effect can be found in the parent application as filed original claim 5 and 25, page 4, fourth from bottom line, Example 2 on page 9, and Example 4 in paragraph [0044], since “[they] all give prominence to dosing at 12 week intervals”.

However, claim 5 and 25, page 4 and fourth from bottom line only recited the 12 week intervals, no results were given.

With regards to Example 2, first, the regimen in Example 2 is different from claimed regimen. Besides, Example 2 recites “[p]reliminary 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”. Thus, Example 2 only shows the results of 12 weeks (3 months) dosing, based on which the skilled person cannot reasonably expect that claimed regimen is effective.

With regards to Example 4, the 12 week dosing appears during the second year (see paragraph [0044]), whereas no therapeutic effects are shown in this period. In fact, from paragraph [0058] and [0044] line 2, only 52 week data (year 1) are shown in Example 4. Thus, the skilled person cannot reasonably expect that claimed regimen is effective.

For the above-mentioned reasons, claims 1 to 14, 16-17 contravene the requirements of Article 83 EPC.

6.3. Clarity (Article 84 EPC)

6.4. Further observations



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Hick, Nora

Date
17-06-2019

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1114 / 3222285
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



ClinicalTrials.gov archive

A service of the U.S. National Institutes of Health

Developed by the National Library of Medicine

← 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 <u>Time Frame: week 52</u> 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

https://clinicaltrials.gov/archive/NCT00637377/2010_11_30[15.05.2017 11:39:04]

	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

**Third Party Observation for application Number
EP20170168808**

Successful submission of observation took place on 12/06/2019
09:43

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

Publication Number: EP3222285

Applicant: REGENERON PHARMA[US]

Date of publication: 27.09.2017

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

Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2) November 30, 2010()

Uploaded documents:

1. NPL1_NPL1_Annex4.pdf

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:

Claims 1-16 are not inventive in view of D1

We fully agree with the European search opinion regarding what D1 has disclosed (see point 4.1 sheet 3 to 4).

Specifically, D1 discloses that 2 mg aflibercept dose intravitreal 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 (see second page, third paragraph).

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline of D1).

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-FcC1(a) to which claim 1 refers.

According to D1, 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 D1.

Novel features not known from the prior art:

The difference between D1 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No supportive evidence

No evidence provided by the present application demonstrates that patients with any one of the above-mentioned disorders will necessarily benefit from the dosage regimen specified in claim 1.

Specifically, Examples 1-4 direct to the treatment of wet age-related macular degeneration (wet AMD), wherein none of the dosage regimen in these Examples comprises “the first five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose” as specified in claim 1.

Example 5 directs to treatment of diabetic macular edema. Specifically, 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).

Example 6 directs to treatment of macular edema secondary to central retinal vein occlusion (CRVO). Specifically, naive patients with macular edema secondary to CRVO received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed (PRN dosing) from Week 24 through Week 52. Thus, the dosage regimen of the Example 6 is as follows: an initial dose at week 0 and four secondary doses at weeks 4, 8, 12, 16 and 20, and then tertiary doses as needed until week 52.

Therefore, no technical effect for the proposed VEGF antagonist and dosage regime in the treatment of AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization has been demonstrated in the present application.

Applicant provided further documents on 26 March 2018 to show that the 12 week dosing that the present claims are based around can be carried out with at least as effective results as those obtained with more frequent dosing. However, Engelbert et al is a post-published document relating to AMD, and other three slides fail to specify the disorder to be treated. Therefore, these post-

filed documents fail to demonstrate the therapeutic effect of the proposed VEGF antagonist towards AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization.

Besides, Engelbert et al is a post-published document, and no evidence shows that the other three slides are available to the skilled person before the effective date of the patent.

According to decision T 1329/04, the verification of whether or not the claimed solution actually solves the problem, i.e. whether the claimed subject-matter actually provides the desired effect, must be based on the data in the application. Post-published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved. (see Case Law of the Boards of Appeal, I. D. 4.6 Solving a technical problem - post-published documents)

Therefore, such four documents filed by applicant should not be considered.

The objective technical problem starting from D1 therefore may be reformulated as provision of alternative therapeutic use and provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FcCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT (see 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) all of which cited in European search opinion sheet 2 to sheet 3), and that adjusting dosing intervals to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D1.

Accordingly, claims 2-13 are not inventive in view of D1. For the similar reasons claims 14-16 are not inventive in view of D1.

5.2. Inventive step (2)

Features known from the prior art:

Claim 17 is not inventive in view of D1 and Annex 4 (NPL1)

Re disclosure of D1, see above.

Novel features not known from the prior art:

The difference between D1 and claim 17 further include three exclusion criteria.

The technical effect caused or technical problems solved by the novel features:

However, the fact that D1 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 D1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

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 (NPL1). 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 paragraph [0050] of the patent. Though claim 17 only select 3 exclusion criteria, 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, 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, claim 17 does not involve an inventive step.

5.3. Inventive step (3)

Features known from the prior art:

Claims 1-17 are not inventive in view of D2

We fully agree with the European search opinion regarding what D2 has disclosed (see point 4.2 sheet 4).

D2 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).

D2 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)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

Novel features not known from the prior art:

The difference between D2 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D2 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FeCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D2.

Accordingly, claims 2-13 are not inventive in view of D2. For the similar reasons claims 14-17 are not inventive in view of D2.

5.4. Inventive step (4)

Features known from the prior art:

Claims 1-17 are not inventive in view of D3

We fully agree with the European search opinion regarding what D3 has disclosed (see point 4.3 sheet 4 to 5).

D3 describes 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 or as needed dosing. Improvements in visual acuity compared to patients receiving laser therapy were reported (§4).

Novel features not known from the prior art:

The difference between D3 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D3 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFR1R2-FeCl(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D3.

Accordingly, claims 2-13 are not inventive in view of D3. For the similar reasons claims 14-17 are not inventive in view of D3.

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)

Re Claims 1 to 13:

Claim 1 has been amended to require that the first FIVE tertiary doses are administered 8 weeks after the immediately preceding dose.

However, claim 5 of the parent application does not directly and unambiguously disclose that amendment. It is apparent that claim 5 of the parent application only recites that the first FOUR tertiary doses, not the first five tertiary doses, are administered 8 weeks after the immediately preceding dose.

In his letter dated March 26, 2018, the applicant alleged that the basis for such amendment is given at paragraph [0043] of the application as filed which refers to the first five tertiary doses being given at such intervals.

However, paragraph [0043] in the present application or in the parent application does not directly and unambiguously disclose that amendment either.

Specifically, first, paragraph [0043] belongs to example 4, thus the condition is age-related macular degeneration, not other angiogenic eye disorder such as diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization. Besides, in paragraph [0043], only 2Q8 regimen seems to be a relevant basis. In 2Q8, 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks, i.e. an initial dose at week 0 and two secondary doses (!) at weeks 4 and 8, and then 5 tertiary doses (!!!) of 2 mg every eight weeks (!).

Accordingly, the application as filed or the parent application does not provide a basis for claims 2 to 13 and

Re Claim 17:

Claim 17 is a dependent claim of claim 1, which further requires that the patient which is selected for treatment does not exhibit the exclusion criteria (1) to (3).

Applicant alleges that basis can be found at least in paragraph [0050] and page 21.

However, neither paragraph [0050] nor page 21 provides basis for new added claim 17.

In fact, paragraph [0050] of the present or the parent application does not directly and unambiguously disclose that only one or some exclusion criteria is to be applied. Rather, it is apparent from the overall context of the example that ALL (!) exclusion criteria listed in this paragraph should be applied when selecting the patient for treatment.

In summary, the Claims 1-13 and 17 do not meet the requirements of Article 76(1) and Article 123(2) EPC.

6.2. Sufficiency of disclosure (Article 83 EPC)

We fully agree with the European search opinion regarding claims 3 and 5-6 additionally contravene the requirements of Art. 83 EPC.

For the same reason new added claim 16 (central retinal vein occlusion) contravenes the requirements of Art. 83 EPC.

Besides, notwithstanding the above Article 76(1), Article 123(2) EPC and Art 56 EPC objections towards claims 1 to 14, 16-17, said claims additionally contravene the requirements of Art. 83 EPC.

When a therapeutic use of a compound is claimed, the therapeutic effect is a technical feature of the claim. Sufficiency of disclosure of a regimen claim requires that the therapeutic effect is either plausible or demonstrated at the filing date.

As discussed above, no therapeutic effect is demonstrated at the filing date. Since the dosing interval extends from 8 weeks to 12 weeks, without further evidence, the skilled person cannot reasonably expect from examples recited in the present specification that such extended interval may have therapeutic effects.

Applicant alleged in “sufficiency” section of his letter dated March 26, 2018 that evidence supporting the plausibility of the therapeutic effect can be found in the parent application as filed original claim 5 and 25, page 4, fourth from bottom line, Example 2 on page 9, and Example 4 in paragraph [0044], since “[they] all give prominence to dosing at 12 week intervals”.

However, claim 5 and 25, page 4 and fourth from bottom line only recited the 12 week intervals, no results were given.

With regards to Example 2, first, the regimen in Example 2 is different from claimed regimen. Besides, Example 2 recites “[p]reliminary 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”. Thus, Example 2 only shows the results of 12 weeks (3 months) dosing, based on which the skilled person cannot reasonably expect that claimed regimen is effective.

With regards to Example 4, the 12 week dosing appears during the second year (see paragraph [0044]), whereas no therapeutic effects are shown in this period. In fact, from paragraph [0058] and [0044] line 2, only 52 week data (year 1) are shown in Example 4. Thus, the skilled person cannot reasonably expect that claimed regimen is effective.

For the above-mentioned reasons, claims 1 to 14, 16-17 contravene the requirements of Article 83 EPC.

6.3. Clarity (Article 84 EPC)

6.4. Further observations



Application No.: 17168808.8

Substantive examination has started on 18.03.20 (see Notice from the European Patent Office dated 29.01.2013, OJ EPO 2013, 153).

For the Examining Division



Europäisches
Patentamt
European
Patent Office
Office européen
des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465



J A Kemp LLP
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME-UNI

Formalities Officer
Name: Striese-Klepe, C
Tel: +49 89 2399 - 2164
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Kling, Isabelle
Tel: +49 89 2399 - 8471

Application No. 17 168 808.8 - 1112	Ref. N400458EP-A	Date 26.03.2020
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).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11 (b) RFees).

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 11.16TRI



Kling, Isabelle
Primary Examiner
For the Examining Division

Enclosure(s): 8 page/s reasons (Form 2906)

Datum
Date 26.03.2020
Date

Blatt
Sheet 1
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

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

Description, Pages

1-22 as originally filed

Claims, Numbers

1-17 filed in electronic form on 26-03-2018

Drawings, Sheets

1/1 as originally filed

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

- D1 Regeneron: "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration",
Regeneron.com
, 22 November 2010 (2010-11-22), XP002770953,
Retrieved from the Internet:
URL:<http://investor.regeneron.com/releasedetail.cfm?releaseid=532099>
[retrieved on 2017-10-09]
- D2 Regeneron: "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)",
regeneron.com
, 20 December 2010 (2010-12-20), XP002770954,
Retrieved from the Internet:
URL:<http://investor.regeneron.com/releasedetail.cfm?releaseid=537916>
[retrieved on 2017-06-09]
- D3 RP: "VEGF Trap",
retinalphysician.com
, 1 March 2010 (2010-03-01), XP002770951,
Retrieved from the Internet:

Datum
Date 26.03.2020
Date

Blatt
Sheet 2
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

URL:<http://www.retinalphysician.com/issues/2010/march-2010/subspecialty-news>
[retrieved on 2017-06-09]

- D4 WO 00/75319 A1 (REGENERON PHARMA [US]; PAPADOPOULOS NICHOLAS J [US]; DAVIS SAMUEL [US]) 14 December 2000 (2000-12-14)
- D5 US 2006/058234 A1 (DALY THOMAS J [US] ET AL) 16 March 2006 (2006-03-16)
- D6 US 2005/260203 A1 (WIEGAND STANLEY J [US] ET AL) 24 November 2005 (2005-11-24)
- D7 NGUYEN Q D ET AL: "A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration",
OPHTHALMOLOGY, J. B. LIPPINCOTT CO., PHILADELPHIA, PA, US,
vol. 116, no. 11, 1 November 2009 (2009-11-01), pages 2141-2148.E1,
XP026732998,
ISSN: 0161-6420, DOI: 10.1016/J.OPHTHA.2009.04.030
[retrieved on 2009-08-22]
- D8 DO DV ET AL.: "An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema.",
BR J OPHTHALMOL,
vol. 93, no. 2, February 2009 (2009-02), pages 144-1449, XP009158490,
- D9 ANANT PAI ET AL.: "Current concepts in intravitreal drug therapy for diabetic retinopathy",
SAUDI JOURNAL OF OPHTHALMOLOGY,
vol. 24, no. 4, 30 June 2010 (2010-06-30), pages 143-149, XP002674122,
- D10 Regeneron Pharmaceuticals, Bayer, New York University: "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting",
Evaluate.com
, 28 September 2008 (2008-09-28), XP002770952,
Retrieved from the Internet:

URL:<http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=165320>
[retrieved on 2017-06-09]

- D11 US 2007/190058 A1 (SHAMS NAVEED [US]) 16 August 2007 (2007-08-16)
- D12 anonymous: "LUCENTIS® (ranibizumab injection) Intravitreal Injection",
, June 2006 (2006-06), pages 1-3, XP002674125,
Retrieved from the Internet:
URL:<http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf>
[retrieved on 2012-04-18]
- D13 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>
- D14 US 2006/172944 A1 (WIEGAND STANLEY J [US] ET AL) 3 August 2006
(2006-08-03)
- 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
- D16 STEWART MW.: "The expanding role of vascular endothelial growth factor
inhibitors in ophthalmology",
MAYO CLIN PROC,
vol. 87, no. 1, January 2012 (2012-01), pages 77-88, XP002674124,
- D17 WO 2012/097019 A1 (REGENERON PHARMA [US]; YANCOPOULOS
GEORGE D [US]) 19 July 2012 (2012-07-19)

1. The only difference between the new claim 1 and previous claim 1 is "five tertiary doses " in line 8 of claim 1.

2. NOVELTY (Articles 52, 54(1) and (2) EPC

The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1, 2, 4, 7-15, 17 is not new within the meaning of Article 54(1) and (2) EPC.

D1 discloses that VEGF Trap-Eye was administered every two months after 3 monthly loading doses (2nd page, 3rd 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, 2 mg monthly, or 2 mg every two months(following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5 mg every month during the first year of 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 dose administered at week 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 treatment lasted **52 WEEKS**, which means that the tertiary dose was administered at least 5 times.

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 D1 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 D1.

Therefore, claims 1, 2, 7 -15 and 17 are not novel over D1.

Claims 1, 4 and 7 to 13, 15 and 17 are not novel over D2:

D2 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).

D2 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)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

Claims 1,4 and 7-13,15 and 17 are not novel in view of D2.

D3 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). The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Claims 1,4 and 7-13, 15 and 17 are not novel in view of D3.

Claims 3, 5 and 6 are novel in the sense of Art. 54 (2) EPC because the specific therapeutic uses of the claimed compound have not been found to be disclosed in the prior art at hand, i.e. 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-Fc ACI (a) encoded by the nucleic acid sequence of SEQ ID NO:1.

3. INVENTIVE STEP (Art. 56 EPC):

Claims 3, 5 and 6 are not inventive in the sense of Art. 56 EPC because:

The closest prior art, D1, describes the successful therapeutic use of the compound and dosage regime as claimed for the treatment of wet age-related macular degeneration.

The difference between D1 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.

The problem to be solved is seen in the provision of alternative therapeutic uses of the claimed compound and dosage regime.

In support of an inventive step the applicant provided Examples 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 VEGF injections showed reduced ocular neovascularization and improvement of visual acuity at week 24 which was maintained through week 52.

The attention of the applicant is drawn to the fact that the claimed diseases have a different nature and etiology than age-related macular degeneration.

It is therefore to be noted that, from the provided evidence, it cannot be concluded that diabetic retinopathy, central retinal vein occlusion or corneal neovascularization patients would necessarily 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 use of the claimed dosages of a VEGF antagonist comprises VEGFR1 R2-Fc ACI (a) encoded by the nucleic acid sequence of SEQID NOR "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-Fc ACI (a) encoded by the nucleic acid sequence of SEQID NOR", which solution would be obvious in view of D1.

The same problem-solution approach would apply taking any of D2, D3, D4, D7, D8, D10, D11, D12, and D13 as closest prior art.

3.7 Alternatively, taking as closest prior art any of D5 or D6 or D9 (VEGF antagonistA/ EGF 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.

3.8 The subject-matter of claims 3, 5 and 6 is therefore not in accordance with the requirements of Art. 56 EPC.

The same problem-solution approach would apply taking any of D2, D3, D4, D7, D8, D10, D11, 12, and D13 as closest prior art.

4. SUFFICIENCY OF DISCLOSURE OF A THERAPEUTIC USE (Art. 83 EPC):

Notwithstanding the above Art 56 EPC objections, claims 3 and 5-6 additionally contravene the requirements of Art. 83 EPC.

When a therapeutic use of a compound is claimed, the therapeutic effect is a technical feature of the claim. Sufficiency of disclosure of a further medical use claim requires that the therapeutic effect is either plausible or demonstrated at the filing date.

This is not the case of claims 3 and 5-6 which rely on technical effects (i.e. treatment of diabetic retinopathy, corneal neovascularization or central retinal vein occlusion) which are neither demonstrated nor plausible for the reasons given in point 3.4-3.6.

5. It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 43(1) EPC. The applicant should also indicate how the subject-matter of the new claim differs from the state of the art and the significance thereof.

At least some of the objections raised above are such that there appears to be no possibility of overcoming them by amendment. **Refusal of the application under Article 97(2) EPC is therefore to be expected.**



BY ONLINE FILING

The European Patent Office
80298 Munich
Germany

13 July 2020

Dear Sirs

European Patent Application No. 17168808.8 - 1112
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP-A DXP

In reply to the Communication of 26 March 2020, please amend the application by replacing the claims at present on file with the new claims attached.

In order to assist in assessing the amendments now being made, please also find attached a copy of the previous claims showing the changes tracked-in.

A copy of the drug label for the VEGF antagonist Eylea is also enclosed, which provides experimental data further illustrating the efficacy of the claimed approach, as discussed further below.

Amendments & Basis

Purely in order to facilitate prosecution, whilst not indicating agreement with the objections raised, a number of amendments are now being made. Please note that the Applicant reserves the right to pursue divisional application(s), including such divisional application(s) directed to subject matter excised from the claims during prosecution.

The main amendments to the claims can be summarised as follows:

- Previous claims 1 to 13, 15, and 16 have been cancelled. The claim numbering and dependencies of subsequent claims have been adjusted appropriately.
- Claim 1 is based on previous claim 14. It has been amended to refer to the further conditions of diabetic retinopathy, diabetic macular edema and choroidal neovascularization. That amendment finds basis in the application as filed, and parent application as filed at, for instance, paragraph [0025].

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • PARIS • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 F +44 20 7430 1000
mail@jakemp.com www.jakemp.com

J A Kemp LLP is a Limited Liability Partnership, registered in England and Wales (registered number OC427581) and regulated by IPReg.
Our registered office is at 14 South Square, Gray's Inn, London WC1R 5JJ, UK. Our use of the word 'partner' refers to a member of J A Kemp LLP.

- Claim 1 has also been amended to specify that the VEGF antagonist is “a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component.” That amendment finds basis in the present and parent applications as filed at, for instance, paragraphs [0023] and [0035].
- New claims 3 to 11 have been added which find basis in the present and parent applications as filed as follows:
 - new claims 3 to 5 at paragraph [0025];
 - new claim 6 at paragraphs [008] and [0028], numbered further embodiment 17 of the present application/original claim 17 of the parent;
 - new claim 7 in numbered further embodiment 19 of the present application/original claim 19 of the parent;
 - new claim 9 in numbered further embodiment 20 of the present application/original claim 20 of the parent; and
 - new claims 9 and 10 in paragraph [0023], as well as numbered further embodiments 11 and 31 of the present application as filed, and original claims 11 and 31 of the parent application as filed.

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

Novelty - Item 2 of the Communication

The subject matter of the amended claims is novel over each of D1 to D3 cited in the Search Opinion for at least the reasons set out below.

Novelty over D1

The subject matter of the amended claims is novel over D1.

D1 does not disclose the claimed dosing regimen comprising a quarterly (12-week) dosing component, as set out in new claim 1. As cited in the Communication, D1 at page 3, third paragraph contains the following discussion:

“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 Communication cites the group in D1 who are given three monthly loading doses and then 2 mg every two months. Even if, as argued in the Communication, the three monthly loading doses are considered to represent the primary and secondary doses recited by claim 1, there is no administration of tertiary doses as required by amended claim 1, **where each tertiary dose is administered 12 weeks after the immediately preceding dose**. In D1 in the group focused on by the Communication the “*tertiary doses*” are given as PRN dosing (*i.e. pro re nata* dosing, which is as needed dosing) somewhere between every month and every three months, but without defining the dosing beyond those intervals. As such, there is no clear and unambiguous disclosure of tertiary dosing at 12 weekly intervals as specified by amended claim 1.

As the subject matter of new claim 1 is novel over D1, that of dependent claims 2 to 11 is also novel over D1.

Novelty over D2

The subject matter of amended claim 1 is also novel over D2. That is the case for at least the reason that **D2 fails to disclose a dosing regimen including a 12-week dosing component** as recited by new claim 1. **Also, D2 does not refer to macular degeneration, diabetic retinopathy, or choroidal neovascularization**. Hence, so far as amended claim 1 refers to those conditions it is novel over D2 for that additional reason.

As the subject matter of amended claim 1 is novel over D2, that of all of the subsequent dependent claims is also novel.

Novelty over D3

The subject matter of the amended claims is also novel over D3 for similar reasons to those outlined above for D1 and D2. In particular, the dosing referred to in D3 of three loading doses at monthly intervals followed by dosing every other month **neither includes dosing 12 weeks apart as recited by claim 1. The subject matter of the amended claims as a whole is therefore novel over D3.**

As the subject matter of amended claim 1 is novel over D3, that of all of the subsequent dependent claims is also novel.

Inventive Step - Item 3 of the Communication

(a) Inventive step for claim 1

The amended claims are now focussed on very specific dosing regimens. New claim 1 is directed to:

“A VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary

dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component.”

Hence, the claimed regimen involves a very specific VEGF antagonist which is given first as an initial dose, then as one or more secondary doses at four weekly spacing, then as tertiary doses each separated by 12 weeks.

The Communication cites D1 as closest prior art and as such D1 will be adopted as closest prior art for the present analysis. The technical problem to be solved may be formulated as the provision of a further therapy for treatment of eye disorders, with the solution to the technical problem as now claimed. The solution to the technical problem would not have been obvious from D1 or indeed any of the cited prior art. In particular, none of the cited art, including D1, discloses or suggests a dosing regimen as now recited by claim 1. **There is no mention at all in D1 of dosing at 12 week intervals within the context of the specific regimen as now set out by claim 1.**

At the time of the invention, the standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month. This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event. **Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention, once a month treatment remained the standard of care.**

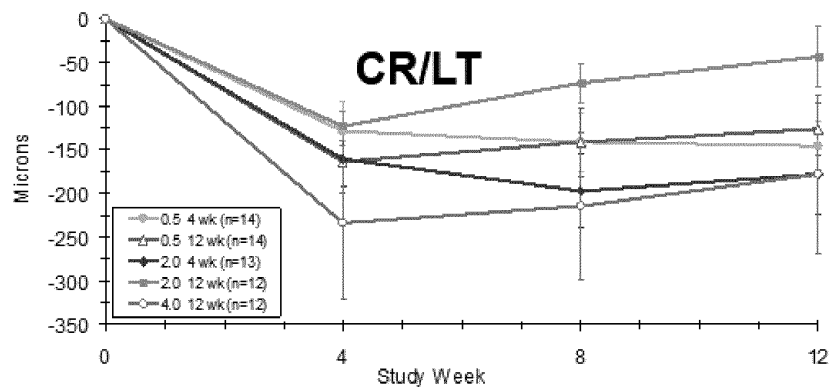
There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, the claimed treatment protocol is not *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month, nor from any of the cited prior art. That the approach claimed by claim 1 is inventive is further confirmed by the unexpected technical advantages demonstrated by Example 2 of the present application.

Example 2 of the present application demonstrates the benefit of dosing at 12 week intervals (“q12w dosing”) which forms part of the regimen now set out by new claim 1. In Example 2, it is demonstrated that amongst the combined q4w and q12w treatment groups, a collective reduction of retinal thickness of 135 microns was observed.

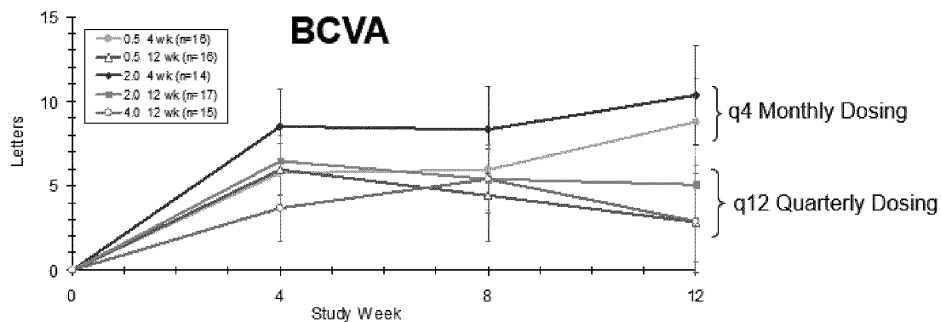
Moreover, Example 2 states that:

“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” Patients receiving only a single dose (the initial dose), before data were collected at the 12 week point, were those in the q12w dosing groups (nos. 2, 4 and 5).”

Additional data from this study, at the 12-week timepoint, further corroborating the validity of the claimed approach are shown below. In the following two graphs, the retinal thickness and visual acuity of subjects in the individual dosing groups are compared:



CR/LT=central retinal/lesion thickness



BCVA=best corrected visual acuity

With respect to BCVA, these data demonstrated that monthly (q4w) and quarterly (q12w) dosing did not result in substantially different results at 8 weeks; even quarterly dosing resulted in substantial improvements at week 8 (range of means: 4.4 to 5.4 letters gained), and at week 12 (range of the means: 2.8 to 5.1 letters gained); that monthly dosing was numerically superior at 12 weeks, though not

statistically significant; and that monthly dosing resulted in continued BCVA improvement through week 12 (range of means at week 12: 8.8 to 10.4 letters gained).

As will be appreciated, **the ability to dose less often as part of an overall regimen, whilst still obtaining good benefit from the therapy is clearly an advance.** That is particularly so in this specific technical field where administration often entails intravitreal injection and so less frequent administration is likely to be of benefit to the patient in terms of having to undergo such invasive injections less often, and due to the increased likelihood of patient compliance given that reduction in terms of the likely reduction in the number of injections needed.

In respect of claim 1, it also reasonable that the technical problem is solved across the full breadth of the claims. As discussed above, Example 2 does show the benefit of 12 week dosing, which forms an integral part of the regimen of new claim 1. No evidence to the contrary has been provided to show that anything covered by claim 1 would not be effective. Hence, what is claimed by claim 1 is inventive both over the cited prior art and in terms of the technical problem being solved across the full breadth of the claim 1.

(b) *Inventive step for claims 2 to 11*

As the subject matter of claim 1 is inventive, that of dependent claims 2 to 11 is also inventive.

Sufficiency of Disclosure - Item 4 of the Communication

As discussed above in relation to the technical problem being solved across the breadth of the claims, the application as filed provides data showing the efficacy of the claimed approach, which is further corroborated by the post-filing data provided, namely the data indicated in the drug label for Eylea.

No evidence calling into doubt what is claimed has been provided, let alone the serious doubts substantiated by verifiable factors needed for any finding of insufficiency. Article 83 EPC is complied with.

Conclusions

It is believed that the objections raised have been overcome. If any remaining points remain the Examiner is welcome to please telephone or to issue a further Communication. Purely as a precaution, in case the Examining Division consider refusing the application, the previous request for Oral Proceedings is maintained.

Please note that the Applicant does not consent to amendments being made to the claims without their prior consultation. Hence, if the Examining Division wish to propose amendments to the claims, the Primary Examiner is asked to please telephone the undersigned so that the Applicant can be consulted.

Yours faithfully

Electronically Signed
DR DAVID POWER
FOR J A KEMP LLP
ASSOCIATION NO. 811

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (afibercept) Injection, for Intravitreal Use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage (1) 5/2019
- Dosage and Administration (2) 8/2019

INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)

DOSAGE AND ADMINISTRATION

- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
 - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
 - Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
 - Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. (2.2)
- **Macular Edema Following Retinal Vein Occlusion (RVO)**
 - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)

- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)**

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- Injection: 2 mg/0.05 mL solution in a single-dose pre-filled syringe (3)
- Injection: 2 mg/0.05 mL solution in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy (DR)

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Injection Instructions
- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
- 2.4 Diabetic Macular Edema (DME)
- 2.5 Diabetic Retinopathy (DR)
- 2.6 Preparation for Administration - Pre-filled Syringe
- 2.7 Preparation for Administration - Vial
- 2.8 Injection Procedure

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Ocular or Periocular Infections
- 4.2 Active Intraocular Inflammation
- 4.3 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Endophthalmitis and Retinal Detachments
- 5.2 Increase in Intraocular Pressure
- 5.3 Thromboembolic Events

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
- 14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)
- 14.4 Diabetic Macular Edema (DME)
- 14.5 Diabetic Retinopathy (DR)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy (DR)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

Pre-filled Syringe: A 30-gauge $\times$ ½-inch sterile injection needle is needed but not provided.

Vial: A 5-micron sterile filter needle (19-gauge $\times$ 1½-inch), a 1-mL Luer lock syringe and a 30-gauge $\times$ ½-inch sterile injection needle are needed.

EYLEA is available packaged as follows:

- Pre-filled Syringe
- Vial Kit with Injection Components (filter needle, syringe, injection needle)

[see *How Supplied/Storage and Handling* (16)].

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see *Clinical Studies* (14.1)]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly) [see *Clinical Studies* (14.2), (14.3)].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see *Clinical Studies* (14.4)]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR)

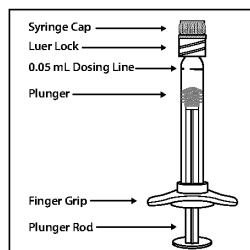
The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see *Clinical Studies* (14.5)]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration - Pre-filled Syringe

The EYLEA pre-filled glass syringe is sterile and for single use only. It should be inspected visually prior to administration. **Do not** use if particulates, cloudiness, or discoloration are visible, or if the package is open or damaged.

The intravitreal injection should be performed with a 30-gauge $\times$ ½-inch injection needle (not provided).

PRE-FILLED SYRINGE DESCRIPTION – Figure 1:



Use aseptic technique to carry out the following steps:

1. PREPARE

When ready to administer EYLEA, open the carton and remove sterilized blister pack. Carefully peel open the sterilized blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. REMOVE SYRINGE

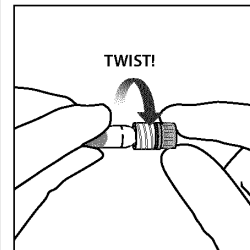
Using aseptic technique, remove the syringe from the sterilized blister pack.

3. TWIST OFF SYRINGE CAP

Twist off the syringe cap by holding the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand (see Figure 2).

Note: To avoid compromising the sterility of the product, do not pull back on the plunger.

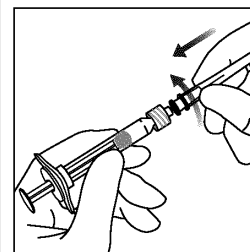
Figure 2:



4. ATTACH NEEDLE

Using aseptic technique, firmly twist a 30-gauge $\times$ ½-inch injection needle onto the Luer lock syringe tip (see Figure 3).

Figure 3:

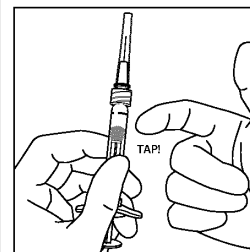


Note: When ready to administer EYLEA, remove the plastic needle shield from the needle.

5. DISLodge AIR BUBBLES

Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

Figure 4:



6. EXPEL AIR AND SET THE DOSE

To eliminate all bubbles and to expel excess drug, slowly depress the plunger rod to align the plunger dome edge (see Figure 5a) with the black dosing line on the syringe (equivalent to 50 microliters) (see Figure 5b).

Figure 5a:

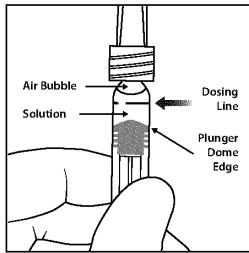
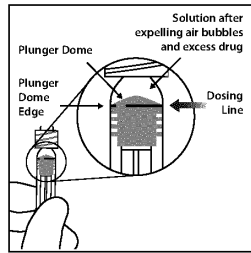


Figure 5b:



7. The pre-filled syringe is for single use only. After injection any unused product must be discarded.

2.7 Preparation for Administration - Vial

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

The glass vial is for single use only.

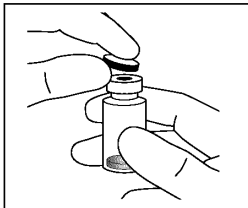
Use aseptic technique to carry out the following preparation steps:

Prepare for intravitreal injection with the following medical devices for single use:

- a 5-micron sterile filter needle (19-gauge $\times$ 1½-inch)
- a 1-mL sterile Luer lock syringe (with marking to measure 0.05 mL)
- a sterile injection needle (30-gauge $\times$ ½-inch)

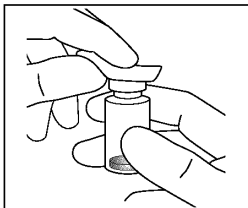
1. Remove the protective plastic cap from the vial (see Figure 6).

Figure 6:



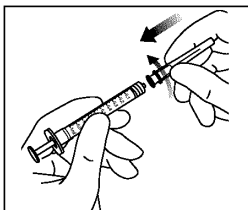
2. Clean the top of the vial with an alcohol wipe (see Figure 7).

Figure 7:



3. Remove the 19-gauge $\times$ 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 8).

Figure 8:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figure 9a and Figure 9b).

Figure 9a:

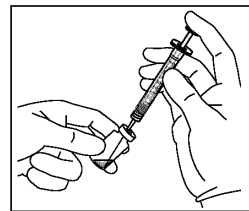
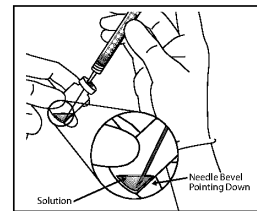


Figure 9b:

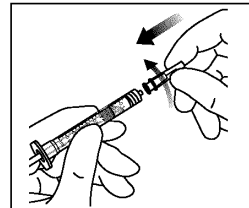


6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle. **Note:** Filter needle is **not** to be used for intravitreal injection.

8. Remove the 30-gauge $\times$ ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 10).

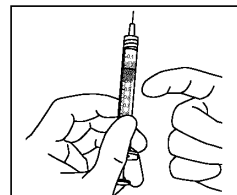
Figure 10:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 11).

Figure 11:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figure 12a and Figure 12b).

Figure 12a:

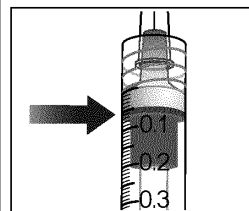
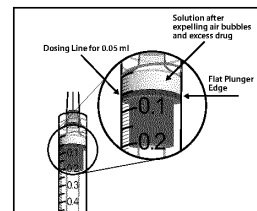


Figure 12b:



2.8 Injection Procedure

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad-spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [see Patient Counseling Information (17)].

Each sterile, pre-filled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new sterile, pre-filled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

EYLEA is a clear, colorless to pale yellow solution available as:

- Injection: 2 mg/0.05 mL in a single-dose pre-filled glass syringe
- Injection: 2 mg/0.05 mL in a single-dose glass vial

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [see Adverse Reactions (6.1)]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [see Dosage and Administration (2.8) and Patient Counseling Information (17)].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [see Adverse Reactions (6.1)]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [see Dosage and Administration (2.8)].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see Contraindications (4.3)]
- Endophthalmitis and retinal detachments [see Warnings and Precautions (5.1)]
- Increase in intraocular pressure [see Warnings and Precautions (5.2)]
- Thromboembolic events [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) [see Clinical Studies (14.1)].

Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT) [see Clinical Studies (14.2), (14.3)].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100 [see *Clinical Studies* (14.4)].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For

these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [see *Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [see *Clinical Pharmacology* (12.1)], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomenocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternbrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥ 65 years of age and approximately 46% (1250/2701) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA (aflibercept) Injection is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose pre-filled glass syringe or a single-dose glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, with a pH of 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions during the first year.

Macular Edema Following Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [see *Clinical Studies* (14.2), (14.3)].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [see *Clinical Studies* (14.4)].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life ($t_{1/2}$) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [see *Clinical Studies* (14)].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multicenter, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Protocol-specified visits occurred every 28±3 days. Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 13 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference ^b (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference ^b in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference ^b (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

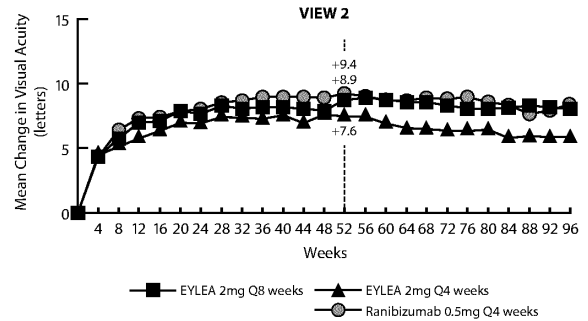
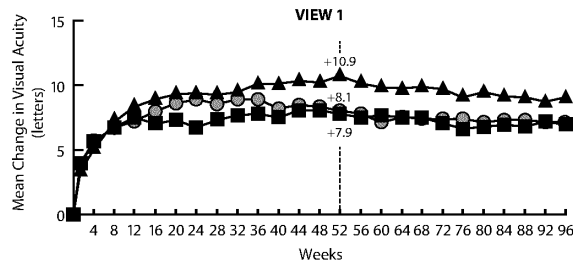
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study

^a After treatment initiation with 3 monthly doses

^b EYLEA group minus the ranibizumab group

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were in general consistent with the results in the overall populations.

Figure 13: Mean Change in Visual Acuity from Baseline to Week 96* in VIEW1 and VIEW2 Studies



*Patient dosing schedules were individualized from weeks 52 to 96 using a modified 12-week dosing regimen.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12 week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 14 below.

Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference ^{a,b} (%) (95.1% CI)		44.8% ^c (32.9, 56.6)		38.3% ^c (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean ^{a,d} (95.1% CI)		21.7 ^c (17.3, 26.1)		14.7 ^c (10.7, 18.7)

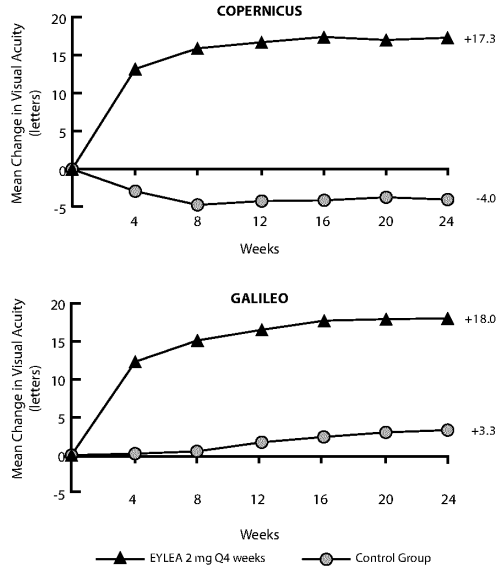
^a Difference is EYLEA 2 mg Q4 weeks minus Control

^b Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study

^c p<0.01 compared with Control

^d LS mean and CI based on an ANCOVA model

Figure 14: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 15 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference ^{a,b} (%) (95% CI)		26.6% ^c (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean ^{a,d} (95% CI)		10.5 ^c (7.1, 14.0)

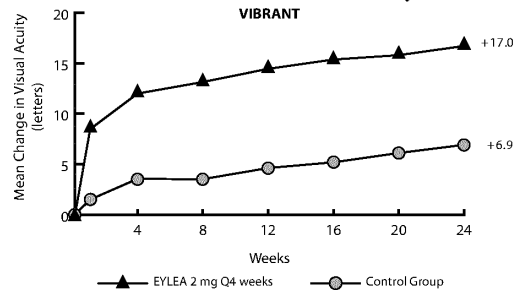
^a Difference is EYLEA 2 mg Q4 weeks minus Control

^b Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

^c p<0.01 compared with Control

^d LS mean and CI based on an ANCOVA model

Figure 15: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 16 below.

Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference ^{b,c} in LS mean (97.5% CI)	9.1 ^d (6.3, 11.8)	9.3 ^d (6.5, 12.0)		10.5 ^d (7.7, 13.2)	12.2 ^d (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference ^{c,e} (%) (97.5% CI)	24.2% ^d (13.5, 34.9)	23.3% ^d (12.6, 33.9)		23.3% ^d (13.5, 33.1)	34.2% ^d (24.1, 44.4)	

Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)
Difference ^{b,c} in LS mean (97.5% CI)	8.2 ^d (5.2, 11.3)	10.7 ^d (7.6, 13.8)		10.1 ^d (7.0, 13.3)	10.6 ^d (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference ^{c,e} (%) (97.5% CI)	19.0% ^d (8.0, 29.9)	26.1% ^d (14.8, 37.5)		20.1% ^d (9.6, 30.6)	25.8% ^d (15.1, 36.6)	

^a After treatment initiation with 5 monthly injections

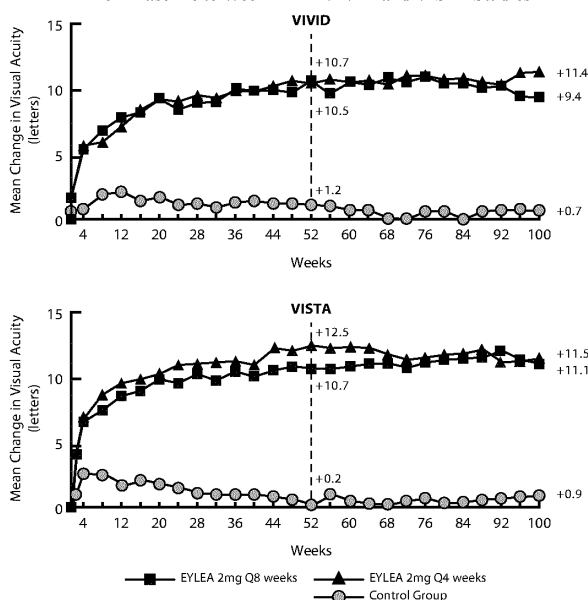
^b LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model

^c Difference is EYLEA group minus Control group

^d p<0.01 compared with Control

^e Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

Figure 16: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

14.5 Diabetic Retinopathy (DR)

Efficacy and safety data of EYLEA in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies.

VIVID AND VISTA

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [see Clinical Studies (14.4)].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 8 below.

Table 8: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients ^b	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	32 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference ^{c,d} (%) (97.5% CI)	24% ^e (12, 36)	21% ^e (9, 33)		22% ^e (11, 33)	22% ^e (11, 33)	

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)

^a After treatment initiation with 5 monthly injections

^b The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline

^c Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

^d Difference is EYLEA minus Control group

^e p<0.01 compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

PANORAMA

The PANORAMA study assessed the safety and efficacy of EYLEA in a randomized, multi-center, double-masked, controlled study in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) (ETDRS-DRSS of 47 or 53), without central-involved DME (CI-DME). A total of 402 randomized patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). Patient ages ranged from 25 to 85 years with a mean of 55.7 years.

Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) 3 initial monthly EYLEA 2 mg injections followed by one injection after 8 weeks and then one injection every 16 weeks (EYLEA 2Q16); 2) 5 monthly EYLEA 2 mg injections followed by one injection every 8 weeks (EYLEA 2Q8); and 3) sham treatment.

The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined EYLEA groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham. A key secondary endpoint was the proportion of patients developing the composite endpoint of proliferative diabetic retinopathy or anterior segment neovascularization through week 52.

At week 52, efficacy in the 2Q16 and 2Q8 groups was superior to the sham group (see Table 9 and Table 10). The proportion of patients with a ≥2-step improvement over time is shown in Figure 17.

Table 9: Proportion of Patients Who Achieved a ≥ 2 -Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 in PANORAMA

	PANORAMA				
	Week 24		Week 52		
	EYLEA Combined	Control (sham)	EYLEA 2Q16	EYLEA 2Q8	Control (sham)
Full Analysis Set	N=269	N=133	N=135	N=134	N=133
Proportion of patients with a ≥ 2 -step improvement on ETDRS-DRSS from Baseline (%)	58%	6%	65%	80%	15%
Adjusted Difference ^a (%) (95% CI) ^b	52% ^c (45, 60)		50% ^c (40, 60)	65% ^c (56, 74)	

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)

^a Difference is EYLEA group minus sham

^b Difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable

^c $p < 0.01$ compared with Control. p -value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable.

Figure 17: Proportion of Patients Who Achieved a ≥ 2 -Step Improvement from Baseline in the ETDRS-DRSS Score Through Week 52 in PANORAMA

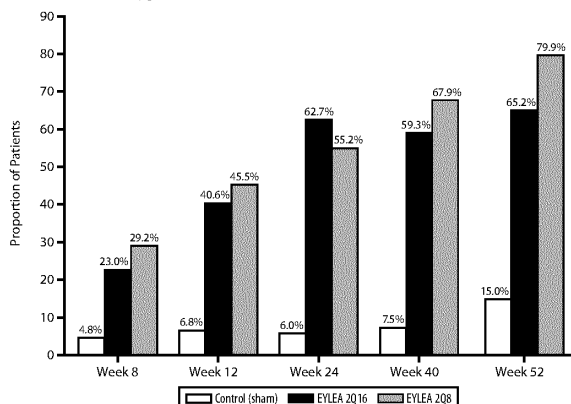


Table 10: Effect of EYLEA on Worsening of Diabetic Retinopathy in PANORAMA through Week 52

	EYLEA 2Q16	EYLEA 2Q8	Control (Sham)
Full Analysis Set	N=135	N=134	N=133
Composite Endpoint of Developing PDR or ASNV ^a			
Event Rate ^b	4.0% ^d	2.4% ^d	20.1%
Hazard Ratio	0.15	0.12	
Development of Proliferative Diabetic Retinopathy ^c			
Event Rate ^b	1.6% ^d	0.0% ^d	11.9%
Hazard Ratio	0.11	0.00	

PDR = Proliferative Diabetic Retinopathy; ASNV = Anterior Segment Neovascularization

^a As diagnosed by either the Reading Center or Investigator through week 52

^b Estimated using Kaplan-Meier method

^c Defined as ≥ 2 -step worsening on the ETDRS-DRSS score through week 52

^d $p < 0.01$ compared with Control

16 HOW SUPPLIED/STORAGE AND HANDLING

Each pre-filled syringe or vial is for single eye use only. EYLEA is supplied in the following presentations [see *Dosage and Administration* (2.6), (2.7), and (2.8)].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-01	Pre-filled Syringe	one blister pack containing one EYLEA 2 mg/0.05 mL sterile, single-dose pre-filled glass syringe one package insert
61755-005-02	Vial Kit with Injection Components	one EYLEA 2 mg/0.05 mL single-dose glass vial one 19-gauge $\times$ 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge $\times$ ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

Refrigerate EYLEA at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [see *Warnings and Precautions* (5.1)].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [see *Adverse Reactions* (6)]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

© 2019, Regeneron Pharmaceuticals, Inc.

All rights reserved.

Revised Date: 08/2019

EYL.19.07.0297



Letter accompanying subsequently filed items

Representative:
J A Kemp LLP
811
14 South Square
Gray's Inn
London Greater London WC1R 5JJ
United Kingdom

Phone: +44 20 3077 8600
Fax: +44 20 7430 1000
E-mail: mail@jakemp.com

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

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

Application number

17168808.8

Applicant's or representative's reference

N400458EP-A

	Description of document	Original file name	Assigned file name
1	Amended claims (clean copy)	Amended claims (clean) Jul20 N400458EP-A DXP.PDF	CLMS-1.PDF
2	Amended claims with annotations	Amended claims (tracked) Jul20 N400458EP-A DXP.pdf	CLMS-HWA-1.pdf
3	Document filed during examination procedure	EYLEA N400458EP-A DXP.PDF	EXAM-1.PDF
4	Reply to examination report	Response Jul20 N400458EP-A DXP.PDF	EXRE3-1.PDF

	Payment	
1	Method of payment	Not specified

Signatures

Place: **London**
Date: **13 July 2020**
Signed by: **David Power 23473**
Association: **J A Kemp LLP**
Representative name: **/David POWER/**
Capacity: **(Representative)**

N400458EP-A

CLAIMS

1. A VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component.
2. The VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient of claim 1, wherein exclusion criteria for the patient to receive the VEGF antagonist include:
 - (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.
3. The VEGF antagonist of claim 1 for use in a method for treating wet age related macular degeneration.
4. The VEGF antagonist of claim 1 for use in a method for treating diabetic retinopathy
5. The VEGF antagonist of claim 1 for use in a method for treating diabetic macular edema.
6. The VEGF antagonist of claim 1 for use in a method for treating choroidal neovascularization.

7. The VEGF antagonist of any one of claims 1-6 wherein the VEGF antagonist is administered to the patient intravitreally.
8. The VEGF antagonist of claim 7 wherein about 0.5 mg of the VEGF antagonist is administered intravitreally to the patient.
9. The VEGF antagonist of claim 7 wherein about 2 mg of the VEGF antagonist is administered intravitreally to the patient.
10. The VEGF antagonist of any one of claims 1-9 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.
11. The VEGF antagonist of claim 10 wherein the VEGF antagonist comprises amino acids 27-457 of SEQ ID NO: 2.

CLAIMS

1. ~~A VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose; wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization; and wherein the VEGF antagonist comprises VEGFR1R2-FcΔC(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.~~
2. ~~The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is age related macular degeneration.~~
3. ~~The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic retinopathy.~~
4. ~~The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is diabetic macular edema.~~
5. ~~The VEGF antagonist for according to claim 1, wherein the angiogenic eye disorder is central retinal vein occlusion.~~
6. ~~The VEGF antagonist for use according to claim 1, wherein the angiogenic eye disorder is corneal neovascularization.~~
7. ~~The VEGF antagonist for use according to any one of the preceding claims, wherein the VEGF antagonist comprises~~

- (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO: 2;
(2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO: 2; and
(3) a multimerization component comprising amino acids 232-457 of SEQ ID NO: 2.

~~8. The VEGF antagonist for use according to any one of the preceding claims, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.~~

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

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

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

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

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

14. A VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist comprises VEGFR1R2-FcΔC(a) encoded by the nucleic acid sequence of SEQ ID NO: 4 is a receptor-based chimeric molecule comprising

an immunoglobulin-like (Ig) domain 2 of VEGFR1,
an Ig domain 3 of VEGFR2, and
a multimerizing component.

~~15. A VEGF antagonist for use in a method for treating diabetic macular edema in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the administration of 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 at least 8 weeks after the immediately preceding dose; and wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.~~

~~16. A VEGF antagonist for use in a method for treating central retinal vein occlusion in a patient, said method comprising sequential administration of a single initial dose of the VEGF antagonist, followed by the administration of four secondary doses of the VEGF antagonist, followed by the use of one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is for administration 4 weeks after the immediately preceding dose; wherein each tertiary dose is for administration at least 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.~~

~~2 17. The VEGF antagonist for use in a method for treating an angiogenic eye disorder in a patient of claim 1, wherein exclusion criteria for the patient to receive the VEGF antagonist include:~~

- ~~(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.~~

3. The VEGF antagonist of claim 1 for use in a method for treating wet age related macular degeneration.

4. The VEGF antagonist of claim 1 for use in a method for treating diabetic retinopathy
5. The VEGF antagonist of claim 1 for use in a method for treating diabetic macular edema.
6. The VEGF antagonist of claim 1 for use in a method for treating choroidal neovascularization.
7. The VEGF antagonist of any one of claims 1-6 wherein the VEGF antagonist is administered to the patient intravitreally.
8. The VEGF antagonist of claim 7 wherein about 0.5 mg of the VEGF antagonist is administered intravitreally to the patient.
9. The VEGF antagonist of claim 7 wherein about 2 mg of the VEGF antagonist is administered intravitreally to the patient.
10. The VEGF antagonist of any one of claims 1-9 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.
11. The VEGF antagonist of claim 10 wherein the VEGF antagonist comprises amino acids 27-457 of SEQ ID NO: 2.



Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	8815724
Application number	EP17168808.8
Date of receipt	13 July 2020
Receiving Office	European Patent Office, The Hague
Your reference	N400458EP-A
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (1 p.) CLMS-HWA-1.pdf Amended claims (tracked) Jul20 N400458EP-A DXP.pdf (4 p.) EXRE3-1.PDF Response Jul20 N400458EP-A DXP.PDF (7 p.) ep-sfd-request.xml CLMS-1.PDF Amended claims (clean) Jul20 N400458EP-A DXP.PDF (2 p.) EXAM-1.PDF EYLEA N400458EP-A DXP.PDF (10 p.)
Submitted by	CN=David Power 23473
Method of submission	Online
Date and time receipt generated	13 July 2020, 12:48 (CEST)
Message Digest	0D:6B:B6:C4:C8:5A:02:E8:E3:91:F2:C7:91:E2:F9:93:25:13:51:68

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/

Acknowledgement of receipt - application number
EP17168808.8

Page 1 of 1

Mylan Exhibit 1067
Mylan v. Regeneron, IPR2022-01226
Page 238

MAIWALD · Eisenstrasse 3 · 80335 München

Europäisches Patentamt

80298 München

**Maiwald Patentanwalts- und
Rechtsanwaltsgesellschaft mbH**

München
Düsseldorf

Elisenhof, Eisenstrasse 3
80335 München
T +49 89 7472660
F +49 89 776424
E
H www.maiwald.eu

Munich, 22 September 2020

Application No.: EP 17 168 808.8
Applicant: Regeneron Pharmaceuticals, Inc.

Dr. Andrea Lasar
Partner
lasar@maiwald.eu

Our ref.: 17061U1035-DIV

Observations pursuant to Article 115 EPC regarding European patent application 17 168 808.8

- ¹ In accordance with Article 115 EPC, Third Party Observations against European patent application EP 17 168 808.8 (EP 3 222 285 A1) are filed on behalf of

bioeq GmbH

Bergfeldstraße 9

83607 Holzkirchen

Germany

- ² For the reasons set forth below, the claims filed with applicant's submission of 13 July 2020 are **not in compliance with the requirements of the EPC.**

Geschäftsführer
(Board of Directors)

Dr. Regina Neuefeind, LL.M.
Lutz Kietzmann, LL.M.
Dr. Norbert Hansen
Dr. Martin Huenges, LL.M.
Dr. Holger Glas, LL.M.
Dr. Dirk Bühler
Dr. Christian Schäfflein
Dr. Alexander Schmitz
Angela Zumstein
Dr. Derk Vos
Dr. Berthold Lux
Dr. Eva Ehlich
Alexander Ortleb
Dr. Andreas Ledi
Dr. Eva Dörner
Dr.-Ing. Sophie Ertl
Dr. Marco Stief, LL.M.
Dr. Ralf Kottische
Dr. Christian Pioch

HRB Nr. 111307
Amtsgericht München

RN:LA

A. Claimed subject-matter

³ Pending claim 1 is directed to:

"A VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component."

⁴ Hence, new claim 1 requires the following doses of the VEGF antagonist:

- a single initial dose;
- one or more secondary doses which are administered **4 weeks** after the immediately preceding dose; and
- one or more tertiary doses which are administered **12 weeks** after the immediately preceding dose.

B. Inadmissible extension

⁵ The claimed combination of secondary and tertiary doses is not directly and unambiguously derivable from the application as originally filed.

⁶ When filing previous claim 14 having the dosage regimen as presently claimed with submission of 26 March 2018, the applicant referred to items 21, 25 and 26 of the "Further Numbered Embodiments of the Invention", as well as paragraphs [0009], [0017], [0061] and Example 4. It is submitted that these passages do not provide a basis for new claim 1.

⁷ In particular, item 21 of the further embodiments refers to one or more tertiary doses which are administered **at least 8 weeks** after the immediately preceding dose and item 25 specifies that **at least 5 tertiary doses** are administered, wherein the first four tertiary doses are administered **8 weeks** after the immediately preceding dose and each

subsequent tertiary dose is administered **8 or 12 weeks** after the immediately preceding dose.

- ⁸ Since new claim 1 does not require that at least 5 tertiary doses are administered and that four of the five tertiary doses are administered 8 weeks after the preceding dose, items 21 and 25 cannot form an adequate basis for new claim 1.
- ⁹ Paragraph [0009] of the application as originally filed describes the prior art dosing for aflibercept which involves injections **every 4 weeks** and **every 8 weeks**, but not every 12 weeks.
- ¹⁰ Paragraph [0017] of the application as originally filed provides several possibilities for the secondary and the tertiary dose from which the dosing every 4 weeks for the secondary dose and every 12 weeks for the tertiary dose had to be selected. Since these selections were made from two lists of considerable length, paragraph [0017] of the application as originally filed cannot form the basis for new claim 1 either.
- ¹¹ Paragraph [0061] of the application as originally filed does not relate to any dosing.
- ¹² Finally, in Example 4 the patients were treated with aflibercept either **every 4 weeks** or **every 4 weeks** followed by administration **every eight weeks**, but not by dosing 12 weeks apart.
- ¹³ Additionally, new claim 1 refers to the treatment wet age related macular degeneration (AMD). The treatment of wet AMD with the claimed dosage regimen is not directly and unambiguously derivable from the application as originally filed. As discussed above, paragraph [0009] of the application as originally filed describes the prior art dosing for aflibercept in the context of wet AMD. The only other references to wet or neovascular AMD can be found in the examples which, however, relate to the use of specific dosage regimens and dosages used and therefore cannot form a basis for the treatment of wet AMD in the context of claim 1.
- ¹⁴ In summary, new claim 1 does not meet the requirements of Article 123(2) EPC.

C. Inventive step and sufficiency of disclosure

- ¹⁵ In its submission the patentee refers to Example 2 of the present application which allegedly demonstrates unexpected technical advantages of the dosing at 12 week intervals.

- ¹⁶ It is respectfully submitted that the data presented in the application do not provide support for such an unexpected technical advantage of a dosing as presently claimed.
- ¹⁷ Although Example 2 describes that there were three treatment arms with 12-week dosing intervals (using dosages of 0.5 mg, 2 mg and 4 mg, respectively), the only data described (but not shown) in Example 2 were obtained after 12 weeks which means that the patients with a 12-week dosing interval received only the initial dose at day 0, but no secondary or tertiary doses at all. Hence, the results described in Example 2 apply only to patients which received one single initial dose and not to patients treated with the claimed dosage regimen. The same applies to the additional data shown in the submission of 13 July 2020.
- ¹⁸ Hence, no conclusion regarding the efficacy of a dosing every twelve weeks can be drawn from these data, let alone any conclusion for the specific dosage regimen claimed which comprises **one initial dose**, one or more **secondary doses** administered administered **4 weeks** after the immediately preceding dose and one or more **tertiary doses** administered **12 weeks** after the immediately preceding dose.
- ¹⁹ In addition, Example 2 specifically relates to the treatment of neovascular AMD which is only one of the conditions listed in pending claim 1 and therefore does not provide any experimental support for the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization.
- ²⁰ With submission of 13 July 2020 the applicant also filed the drug label for Eylea® and argued that the efficacy of the claimed approach is further corroborated by this document without referring to any specific passage therein.
- ²¹ It is herewith submitted that the drug label is not relevant for the claimed dosing at all, as it does not relate to the claimed dosing at all. For neovascular (wet) AMD the recommended dose is given as 2 mg **every 4 weeks** for the first 3 months, followed by a dosage of 2 mg **every 8 weeks**. It is mentioned that patients may also be treated with one dose every 12 weeks **after one year of effective therapy**, but this is not as effective as the every 8 week dosing (see section "Dosage and Administration" on page 1, left-hand column of the drug label).
- ²² Hence, according to the drug label a dosing every 12 weeks is only possible under very specific circumstances, namely after one year of effective therapy which means administration every 4 weeks for the first

three months and every 4 or 8 weeks after the first three months for the rest of the year.

- ²³ In contrast, pending claim 1 allows the administration of only one secondary dose 4 weeks after the initial dose and then administration of one or more tertiary doses every 12 weeks which differs considerably from the possibility provided by the drug label.
- ²⁴ For the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization, the possibility of a dosing every 12 weeks is not provided on the drug label at all.
- ²⁵ Accordingly, the Eylea® drug label does not provide support for the claimed dosage regimen either.

D. Conclusions

- ²⁶ The subject-matter of the claims on file does not meet the requirements of Article 123(2) EPC. Additionally, the specific dosage regimen claimed does not involve an inventive step and is not sufficiently disclosed.
- ²⁷ Thus, all requests on file do not meet the requirements of the EPC.

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

electronically signed

Dr. Andrea Lasar
Patentanwältin | European Patent Attorney



Letter accompanying subsequently filed items

Representative:

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH
Andrea Lasar
174
Elisenhof
Elisenstraße 3
80335 München
Germany

Phone: +49 (89) 7472660
Fax: +49 (89) 776424
E-mail: teamL05@maiwald.eu

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

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

Application number

17168808.8

Applicant's or representative's reference

17061U1035-DIV

	Description of document	Original file name	Assigned file name
1	Observations by third parties (Art. 115 EPC)	17061U1035-DIV - Submission.pdf	TIPA1-1.pdf

	Payment	
1	Method of payment	Not specified

Signatures

Place: **Munich**
Date: **22 September 2020**
Signed by: **Andrea Lasar 13617**
Association: **Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH**
Representative name: **Andrea Lasar**
Capacity: **(Representative)**

17061U1035-DIV



Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	9043045	
Application number	EP17168808.8	
Date of receipt	22 September 2020	
Receiving Office	European Patent Office, The Hague	
Your reference	17061U1035-DIV	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (1 p.)	ep-sfd-request.xml TIPA1-1.pdf\17061U1035-DIV - Submission.pdf (5 p.)
Submitted by	CN=Andrea Lasar 13617	
Method of submission	Online	
Date and time receipt generated	22 September 2020, 17:01 (CEST)	
Message Digest	DF:7E:34:E6:8D:FA:34:29:98:55:52:AE:6D:0C:E9:58:92:52:7C:09	

/European Patent Office/



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp LLP
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Formalities officer
Brell, Eva

Date
28.09.2020

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1112 / 3222285
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



MAIWALD · Eisenstrasse 3 · 80335 München

Europäisches Patentamt

80298 München

**Maiwald Patentanwalts- und
Rechtsanwaltsgesellschaft mbH**

München
Düsseldorf

Elisenhof, Eisenstrasse 3
80335 München
T +49 89 7472660
F +49 89 776424
E
H www.maiwald.eu

Munich, 22 September 2020

Application No.: EP 17 168 808.8
Applicant: Regeneron Pharmaceuticals, Inc.

Dr. Andrea Lasar
Partner
lasar@maiwald.eu

Our ref.: 17061U1035-DIV

Observations pursuant to Article 115 EPC regarding European patent application 17 168 808.8

- ¹ In accordance with Article 115 EPC, Third Party Observations against European patent application EP 17 168 808.8 (EP 3 222 285 A1) are filed on behalf of

bioeq GmbH

Bergfeldstraße 9

83607 Holzkirchen

Germany

- ² For the reasons set forth below, the claims filed with applicant's submission of 13 July 2020 are **not in compliance with the requirements of the EPC.**

Geschäftsführer
(Board of Directors)

Dr. Regina Neuefeind, LL.M.
Lutz Kietzmann, LL.M.
Dr. Norbert Hansen
Dr. Martin Huenges, LL.M.
Dr. Holger Glas, LL.M.
Dr. Dirk Bühler
Dr. Christian Schäfflein
Dr. Alexander Schmitz
Angela Zumstein
Dr. Derk Vos
Dr. Berthold Lux
Dr. Eva Ehlich
Alexander Ortleb
Dr. Andreas Ledi
Dr. Eva Dörner
Dr.-Ing. Sophie Ertl
Dr. Marco Stief, LL.M.
Dr. Ralf Kottische
Dr. Christian Pioch

HRB Nr. 111307
Amtsgericht München

RN:LA

A. Claimed subject-matter

³ Pending claim 1 is directed to:

"A VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component."

⁴ Hence, new claim 1 requires the following doses of the VEGF antagonist:

- a single initial dose;
- one or more secondary doses which are administered **4 weeks** after the immediately preceding dose; and
- one or more tertiary doses which are administered **12 weeks** after the immediately preceding dose.

B. Inadmissible extension

⁵ The claimed combination of secondary and tertiary doses is not directly and unambiguously derivable from the application as originally filed.

⁶ When filing previous claim 14 having the dosage regimen as presently claimed with submission of 26 March 2018, the applicant referred to items 21, 25 and 26 of the "Further Numbered Embodiments of the Invention", as well as paragraphs [0009], [0017], [0061] and Example 4. It is submitted that these passages do not provide a basis for new claim 1.

⁷ In particular, item 21 of the further embodiments refers to one or more tertiary doses which are administered **at least 8 weeks** after the immediately preceding dose and item 25 specifies that **at least 5 tertiary doses** are administered, wherein the first four tertiary doses are administered **8 weeks** after the immediately preceding dose and each

subsequent tertiary dose is administered **8 or 12 weeks** after the immediately preceding dose.

- ⁸ Since new claim 1 does not require that at least 5 tertiary doses are administered and that four of the five tertiary doses are administered 8 weeks after the preceding dose, items 21 and 25 cannot form an adequate basis for new claim 1.
- ⁹ Paragraph [0009] of the application as originally filed describes the prior art dosing for aflibercept which involves injections **every 4 weeks** and **every 8 weeks**, but not every 12 weeks.
- ¹⁰ Paragraph [0017] of the application as originally filed provides several possibilities for the secondary and the tertiary dose from which the dosing every 4 weeks for the secondary dose and every 12 weeks for the tertiary dose had to be selected. Since these selections were made from two lists of considerable length, paragraph [0017] of the application as originally filed cannot form the basis for new claim 1 either.
- ¹¹ Paragraph [0061] of the application as originally filed does not relate to any dosing.
- ¹² Finally, in Example 4 the patients were treated with aflibercept either **every 4 weeks** or **every 4 weeks** followed by administration **every eight weeks**, but not by dosing 12 weeks apart.
- ¹³ Additionally, new claim 1 refers to the treatment wet age related macular degeneration (AMD). The treatment of wet AMD with the claimed dosage regimen is not directly and unambiguously derivable from the application as originally filed. As discussed above, paragraph [0009] of the application as originally filed describes the prior art dosing for aflibercept in the context of wet AMD. The only other references to wet or neovascular AMD can be found in the examples which, however, relate to the use of specific dosage regimens and dosages used and therefore cannot form a basis for the treatment of wet AMD in the context of claim 1.
- ¹⁴ In summary, new claim 1 does not meet the requirements of Article 123(2) EPC.

C. Inventive step and sufficiency of disclosure

- ¹⁵ In its submission the patentee refers to Example 2 of the present application which allegedly demonstrates unexpected technical advantages of the dosing at 12 week intervals.

- ¹⁶ It is respectfully submitted that the data presented in the application do not provide support for such an unexpected technical advantage of a dosing as presently claimed.
- ¹⁷ Although Example 2 describes that there were three treatment arms with 12-week dosing intervals (using dosages of 0.5 mg, 2 mg and 4 mg, respectively), the only data described (but not shown) in Example 2 were obtained after 12 weeks which means that the patients with a 12-week dosing interval received only the initial dose at day 0, but no secondary or tertiary doses at all. Hence, the results described in Example 2 apply only to patients which received one single initial dose and not to patients treated with the claimed dosage regimen. The same applies to the additional data shown in the submission of 13 July 2020.
- ¹⁸ Hence, no conclusion regarding the efficacy of a dosing every twelve weeks can be drawn from these data, let alone any conclusion for the specific dosage regimen claimed which comprises **one initial dose**, one or more **secondary doses** administered administered **4 weeks** after the immediately preceding dose and one or more **tertiary doses** administered **12 weeks** after the immediately preceding dose.
- ¹⁹ In addition, Example 2 specifically relates to the treatment of neovascular AMD which is only one of the conditions listed in pending claim 1 and therefore does not provide any experimental support for the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization.
- ²⁰ With submission of 13 July 2020 the applicant also filed the drug label for Eylea® and argued that the efficacy of the claimed approach is further corroborated by this document without referring to any specific passage therein.
- ²¹ It is herewith submitted that the drug label is not relevant for the claimed dosing at all, as it does not relate to the claimed dosing at all. For neovascular (wet) AMD the recommended dose is given as 2 mg **every 4 weeks** for the first 3 months, followed by a dosage of 2 mg **every 8 weeks**. It is mentioned that patients may also be treated with one dose every 12 weeks **after one year of effective therapy**, but this is not as effective as the every 8 week dosing (see section "Dosage and Administration" on page 1, left-hand column of the drug label).
- ²² Hence, according to the drug label a dosing every 12 weeks is only possible under very specific circumstances, namely after one year of effective therapy which means administration every 4 weeks for the first

three months and every 4 or 8 weeks after the first three months for the rest of the year.

- ²³ In contrast, pending claim 1 allows the administration of only one secondary dose 4 weeks after the initial dose and then administration of one or more tertiary doses every 12 weeks which differs considerably from the possibility provided by the drug label.
- ²⁴ For the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization, the possibility of a dosing every 12 weeks is not provided on the drug label at all.
- ²⁵ Accordingly, the Eylea® drug label does not provide support for the claimed dosage regimen either.

D. Conclusions

- ²⁶ The subject-matter of the claims on file does not meet the requirements of Article 123(2) EPC. Additionally, the specific dosage regimen claimed does not involve an inventive step and is not sufficiently disclosed.
- ²⁷ Thus, all requests on file do not meet the requirements of the EPC.

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH

electronically signed

Dr. Andrea Lasar
Patentanwältin | European Patent Attorney



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



Formalities officer
Brell, Eva

Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH
Elisenhof, Eisenstrasse 3
80335 München
Allemagne

Date
28.09.2020

Reference 17061U1035-DIV	Application No./Patent No. 17168808.8 - 1112 / 3222285
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Acknowledgment of receipt of observations by third parties (Article 115 EPC)

Receipt of your letter dated 22.09.2020 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





Europäisches
Patentamt
European
Patent Office
Office européen
des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465



J A Kemp LLP
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME-UNI

Formalities Officer
Name: Braat, B
Tel: +49 89 2399 - 5606
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Kling, Isabelle
Tel: +49 89 2399 - 8471

Application No. 17 168 808.8 - 1112	Ref. N400458EP-A	Date 23.02.2021
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 11.16TRI



Kling, Isabelle
Primary Examiner
For the Examining Division

Enclosure(s): 14 page/s reasons (Form 2906)

Datum
Date 23.02.2021
Date

Blatt
Sheet 1
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

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

Description, Pages

1-22 as originally filed

Claims, Numbers

1-11 filed in electronic form on 13-07-2020

Drawings, Sheets

1/1 as originally filed

A. The third-party observation received on 22/09/2020 pursuant to Art. 115 EPC, calls into question the patentability of the subject-matter claimed for the reasons given below.

1. Art. 123(2) EPC

Amended **claim 1** relates to a VEGF antagonist for use in a method for treating wet age related macular degeneration, diabetic retinopathy, diabetic macular edema or choroidal neovascularization in a patient, the method comprising sequentially administering to the patient a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; and wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and multimerizing component.

The claimed combination of secondary and tertiary doses is not directly and unambiguously derivable from the application as originally filed.

When filing previous claim 14 having the dosage regimen as presently claimed with submission of 26 March 2018, the applicant referred to items 21, 25 and 26 of the "Further Numbered Embodiments of the Invention", as well as paragraphs [0009], [0017], [0061] and Example 4. It is submitted that these passages do not provide a basis for new claim 1.

In particular, item 21 of the further embodiments refers to one or more tertiary doses which are administered at least 8 weeks after the immediately preceding dose and item 25 specifies that at least 5 tertiary doses are administered, wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose and each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

Since new claim 1 does not require that at least 5 tertiary doses are administered and that four of the five tertiary doses are administered 8 weeks after the preceding dose, items 21 and 25 cannot form an adequate basis for new claim 1.

Paragraph [0009] of the application as originally filed describes the prior art dosing for aflibercept which involves injections every 4 weeks and every 8 weeks, but not every 12 weeks.

Paragraph [0017] of the application as originally filed provides several possibilities for the secondary and the tertiary dose from which the dosing every 4 weeks for the secondary dose and every 12 weeks for the tertiary dose had to be selected. Since these selections were made from two lists of considerable length, paragraph [0017] of the application as originally filed cannot form the basis for new claim 1 either.

Paragraph [0061] of the application as originally filed does not relate to any dosing.

Finally, in Example 4 the patients were treated with aflibercept either every 4 weeks or every 4 weeks followed by administration every eight weeks, but not by dosing 12 weeks apart.

Additionally, new claim 1 refers to the treatment **wet age related macular degeneration (AMD)**. The treatment of **wet AMD** with the claimed dosage regimen is not directly and unambiguously derivable from the application as originally filed. As discussed above, paragraph [0009] of the application as originally filed describes the prior art dosing for **afibercept in the context of wet AMD**. The only other references to wet or neovascular AMD can be found in the examples which, however, relate to the use of specific dosage regimens and dosages used and therefore cannot form a basis for the treatment of wet AMD in the context of claim 1.

In summary, new claim 1 does not meet the requirements of Article 123(2) EPC.

2. Inventive step and sufficiency of disclosure

In its submission the patentee refers to Example 2 of the present application which allegedly demonstrates unexpected technical advantages of the dosing at 12 week intervals.

However, the data presented in the application do not provide support for such an unexpected technical advantage of a dosing as presently claimed.

Although Example 2 describes that there were three treatment arms with 12-week dosing intervals (using dosages of 0.5 mg, 2 mg and 4 mg, respectively), the only data described (but not shown) in Example 2 were obtained **after 12 weeks** which means that the patients with a 12-week dosing interval received only the initial dose at day 0, but no secondary or tertiary doses at all. Hence, the results described in Example 2 apply only to patients which received **one single initial dose** and not to patients treated with the claimed dosage regimen. The same applies to the additional data shown in the submission of 13 July 2020.

Hence, **no conclusion** regarding **the efficacy of a dosing every twelve weeks** can be drawn from these data, let alone any conclusion for the specific dosage regimen claimed which comprises one initial dose, one or more secondary doses administered administered 4 weeks after the immediately preceding dose and one or more tertiary doses administered 12 weeks after the immediately preceding dose.

In addition, Example 2 specifically relates to the treatment of **neovascular AMD** which is only one of the conditions listed in pending claim 1 and therefore does not provide any experimental support for the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization.

With submission of 13 July 2020 the applicant also filed the drug label for Eylea® and argued that the efficacy of the claimed approach is further corroborated by this document without referring to any specific passage therein.

However, it appears that the drug label is not relevant for the claimed dosing at all, as it does not relate to the claimed dosing at all. For **neovascular (wet) AMD** the recommended dose is given as 2 mg **every 4 weeks** for the first 3 months, followed by a dosage of 2 mg **every 8 weeks**. It is mentioned that patients may also be treated with one dose every 12 weeks **after one year of effective therapy**, but this is not as effective as the every 8 week dosing (see section "Dosage and Administration" on page 1, left-hand column of the drug label).

Hence, according to the drug label a dosing every 12 weeks is only possible under very specific circumstances, namely after one year of effective therapy which means administration every 4 weeks for the first three months and every 4 or 8 weeks after the first three months for the rest of the year.

In contrast, pending claim 1 allows the administration of only one secondary dose 4 weeks after the initial dose and then administration of one or more tertiary doses every 12 weeks which differs considerably from the possibility provided by the drug label.

For the other conditions listed in pending claim 1, i.e. diabetic retinopathy, diabetic macular edema and choroidal neovascularization, the possibility of a dosing every 12 weeks is not provided on the drug label at all.

Accordingly, the Eylea® drug label does not provide support for the claimed dosage regimen either.

Conclusions

The subject-matter of the claims on file does not meet the requirements of Article 123(2) EPC. Additionally, the specific dosage regimen claimed does not involve an inventive step and is not sufficiently disclosed.

Thus, all requests on file do not meet the requirements of the EPC.

B. The first third-party observation received on 12/06/2019 pursuant to Art. 115 EPC, calls into question the patentability of the subject-matter claimed for the reasons given below; in particular document D1 and the non patent literature document NPL1_Annex4.pdf.

Thus, document NPL1 will be taken into account in the proceedings (see Guidelines E-VI, 3) and the numbering will be adhered to in the rest of the procedure.

3.1. Lack of inventive step

The third Party fully agree with the European Search opinion regarding what **D1 disclosed** (see item 4.1 of the ESOP)

Specifically, D1 discloses that 2mg aflibercept dose intravitreal 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 (see second page, third paragraph).

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

The VEGF Trap-Eye was used to treat wet age-related macular degeneration (see first page, first paragraph and headline of D1).

VEGF Trap-Eye is aflibercept ophthalmic solution (see first page, first paragraph of Annex I). According to paragraph [0007] of WO 2012/097019 (D17), Aflibercept is the same molecule as VEGFR1 R2-FcΔC1 (a) to which claim 1 (as filed 28/03/2018) refers.

According to D1, 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 end point 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.

Furthermore: Table 1 presented in Example 4 of the present application is shown on page 2 of D1.

Novel features not known from the prior art:

The difference between D1 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

No supportive evidence

No evidence provided by the present application demonstrates that patients with any one of the above-mentioned disorders will necessarily benefit from the dosage regimen specified in claim 1.

Specifically, Examples 1-4 are directed to the treatment of wet age-related macular degeneration (wet AMD), wherein none of the dosage regimen in these Examples comprises "the first five tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 12 weeks after the immediately preceding dose" as specified in claim 1.

Datum
Date 23.02.2021
Date

Blatt
Sheet 7
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

Example 5 is directed to treatment of diabetic macular edema. Specifically, 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).

Example 6 is directed to treatment of macular edema secondary to central retinal vein occlusion (CRVO). Specifically, naive patients with macular edema secondary to CRVO received VEGFT intravitreal injections once every four weeks from Week 0 through Week 20, followed by intravitreal VEGFT as needed (PRN dosing) from Week 24 through Week 52. Thus, the dosage regimen of the Example 6 is as follows: an initial dose at week 0 and four secondary doses at weeks 4, 8, 12, 16 and 20, and then tertiary doses as needed until week 52.

Therefore, no technical effect for the proposed VEGF antagonist and dosage regime in the treatment of AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization has been demonstrated in the present application.

Applicant provided further documents on 26 March 2018 to show that the 12 week dosing that the present claims are based around can be carried out with at least as effective results as those obtained with more frequent dosing. However, Engelbert et al. is a post-published document relating to AMD, and other three slides fail to specify the disorder to be treated. Therefore, these post-filed documents fail to demonstrate the therapeutic effect of the proposed VEGF antagonist towards AMD, diabetic macular edema, diabetic retinopathy, central retinal vein occlusion or corneal neovascularization.

Besides, Engelbert et al. is a post-published document, and no evidence shows that the other three slides are available to the skilled person before the effective date of the patent.

According to decision T 1329/04, the verification of whether or not the claimed solution actually solves the problem, i.e. whether the claimed subject-matter actually provides the desired effect, must be based on the data in the application. Post-published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved, (see Case Law of the Boards of Appeal, I.D. 4.6 Solving a technical problem - post-published documents)

Therefore, such four documents filed by applicant should not be considered.

The objective technical problem starting from D1 therefore may be reformulated as the provision of an alternative therapeutic use and the provision of alternative dosage of a VEGF antagonist comprises VEGFR1 R2-FcΔC1 (a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT (see D5 or D6 or D9 (VEGF antagonist/VEGF Trap for treating diabetic retinopathy), D14 (VEGF Trap for treating conical neovascularization) or D15 (VEGF antagonist for treating macular edema secondary to central retinal vein occlusion) all of which cited in European search opinion sheet 2 to sheet 3), and that adjusting dosing intervals to evaluate therapeutic efficacy is a pail of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D1.

Accordingly, claims 2-13 are not inventive in view of D1. For the similar reasons claims 14-16 are not inventive in view of D1.

3.2. Inventive step (2)

Features known from the prior art:

Claim 2 is not inventive in view of D1 and Annex 4 (NPL1)

Re disclosure of D1, see above.

Novel features not known from the prior art:

The difference between D1 and claim 2 further include three exclusion criteria.

The technical effect caused or technical problems solved by the novel features:

However, the fact that D1 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 D1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

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 (NPL1).

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 paragraph [0050] of the patent.

Though, claim 2 (or claim 17 from 28/03/2018) only select 3 exclusion criteria, 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-Irap.

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 [10049] of the application). In particular, to be eligible for the study subjects were required to have subfoveal 1 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, claim 2 does not involve an inventive step.

3.3. Inventive step (3)

Features known from the prior art:

Claims 1-11 are not inventive in view of D2

As said in the European search opinion, D2 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).

D2 reports that “the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary end point 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)

The treatment lasted 52 weeks, which means that the tertiary dose was administered at least 5 times.

Furthermore, Table 2 presented in Example 5 of the present application is shown on page 2 of D2.

Novel features not known from the prior art:

The difference between D2 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

Datum
Date 23.02.2021
Date

Blatt
Sheet 11
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D2 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFR1 R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D2.

Accordingly, claims 2-11 are not inventive in view of D2.

3.4. Inventive step

Claims 1-11 are not inventive in view of D3

As written in the European search opinion (see point 4.3 sheet 4 to 5), D3 describes 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, week 4 and 8) followed through 24 weeks by either dosing every 8 weeks or as needed dosing. Improvements in visual acuity compared to patients receiving laser therapy were reported (§4).

The difference between D3 and claim 1 lies in the fact that (1) dosage regime is different, and that (2) the disorders in claim 1 also comprise diabetic retinopathy, AMD, central retinal vein occlusion or corneal neovascularization.

The technical effect caused or technical problems solved by the novel features:

Datum
Date 23.02.2021
Date

Blatt
Sheet 12
Feuille

Anmelde-Nr:
Application No: 17 168 808.8
Demande n°:

No evidence provided by the present application demonstrates the technical effect of claim 1.

The objective technical problem starting from D3 therefore may be reformulated as provision of alternative dosage of a VEGF antagonist comprises VEGFRIR2-Fc(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:

Since that diabetic retinopathy, diabetic macular edema, central retinal vein occlusion or corneal neovascularization are disorders can be treated with VEGFT, and that adjusting dosing intervals and determining the exclusion criteria for the patient to evaluate therapeutic efficacy is a part of routine practice and does not requires a considerable amount of experimentation, claim 1 is obvious in view of D3.

Accordingly, claims 2-11 are not inventive in view of D3.

4. Any further Observations, e.g. Articles 52(2), 53, 57, 76, 83, 84, 123(2) EPC, validity of the priority date

4.1. Unallowable amendments (Articles 76 and 123 EPC)

See part 1. above.

Specifically, first, paragraph [0043] belongs to example 4, thus the condition is age-related macular degeneration, other angiogenic eye disorder such as diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization. Besides, in paragraph (0043), only 2Q8 regimen seems to be a relevant basis. In 2Q8, 2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks, i.e. an initial dose at week 0 and two secondary doses (!) at weeks 4 and 8, and then 5 tertiary doses (!!!) of 2 mg every eight weeks (!).

Claim 2 (Claim 17 26/03/2018) is a dependent claim of claim 1, which further requires that the patient which is selected for treatment does not exhibit the exclusion criteria (1) to (3).

Applicant alleges that basis can be found at least in paragraph [00501 and page 21.

However, neither paragraph [00501 nor page 21 provides basis for new added claim 2.

In fact, paragraph [0050] of the present or the parent application does not directly and unambiguously disclose that only one or some exclusion criteria is to be applied. Rather, it is apparent from the overall context of the example that ALL (!) exclusion criteria listed in this paragraph should be applied when selecting the patient for treatment.

In summary, the Claims 1-11 do not meet the requirements of Article 76(1) and Article 123(2) EPC.

4.2. Sufficiency of disclosure (Article 83 EPC)

The European search opinion regarding claims 4 and 6 additionally contravene the requirements of Art. 83 EPC.

Besides, notwithstanding the above Article 76(1), Article 123(2) EPC and Art 56 EPC objections towards claims 1 to 11, said claims additionally contravene the requirements of Art. 83 EPC.

When a therapeutic use of a compound is claimed, the therapeutic effect is a technical feature of the claim. Sufficiency of disclosure of a regimen claim requires that the therapeutic effect is either plausible or demonstrated at the filing date.

As discussed above, no therapeutic effect is demonstrated at the filing date. Since the dosing interval extends from 8 weeks to 12 weeks, without further evidence, the skilled person cannot reasonably expect from examples recited in the present specification that such extended interval may have therapeutic effects.

Applicant alleged in “sufficiency” section of his letter dated March 26, 2018 that evidence supporting the plausibility of the therapeutic effect can be found in the parent application as filed original claim 5 and 25, page 4, fourth from bottom line. Example 2 on page 9, and Example 4 in paragraph [0044], since “[they] all give prominence to dosing at 12 week intervals”.

However, claim 5 and 25, page 4 and fourth from bottom line only recited the 12 week intervals, no results were given.

With regards to Example 2, first, the regimen in Example 2 is different from claimed regimen. Besides, Example 2 recites “[preliminary data from a pre-planned interim analysis indicated that VEGFT met its primary end point of a statistically significant reduction in retinal thickness after 12 weeks compared with baseline”. Thus, Example 2 only shows the results of 12 weeks (3 months) dosing, based on which the skilled person cannot reasonably expect that claimed regimen is effective.

With regards to Example 4, the 12 week dosing appears during the second year (see paragraph [0044]), whereas no therapeutic effects are shown in this period. In fact, from paragraph [0058] and [0044] line 2, only 52 week data (year 1) are shown in Example 4. Thus, the skilled person cannot reasonably expect that claimed regimen is effective.

For the above-mentioned reasons, claims 1 to 11 contravene the requirements of Article 83 EPC.

5. At least some of the objections raised above are such that there appears to be no possibility of overcoming them by amendment. **Refusal of the application under Article 97(2) EPC is therefore to be expected.**

J A • K E M P

BY ONLINE FILING

The European Patent Office
80298 Munich
Germany

21 June 2021

European Patent Application No. 17168808.8
REGENERON PHARMACEUTICALS, INC.
Our Ref: N400458EP-A DXP/EE11

We request a two-month extension to the term for replying to the communication pursuant to Article 94(3) EPC dated **23 February 2021**.

Please confirm in due course that this request has been granted.

Electronically Signed
DR DAVID POWER
FOR J A KEMP LLP
ASSOCIATION NO. 811

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • PARIS • OXFORD • CAMBRIDGE • MUNICH
14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 **F** +44 20 7430 1000
mail@jakemp.com **www.jakemp.com**

J A Kemp LLP is a Limited Liability Partnership, registered in England and Wales (registered number OC427581) and regulated by IPReg.
Our registered office is at 14 South Square, Gray's Inn, London WC1R 5JJ, UK. Our use of the word 'partner' refers to a member of J A Kemp LLP.



Letter accompanying subsequently filed items

Representative:
J A Kemp LLP
811
14 South Square
Gray's Inn
London Greater London WC1R 5JJ
United Kingdom

Phone: +44 20 3077 8600
Fax: +44 20 7430 1000
E-mail: mail@jakemp.com

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

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

Application number

17168808.8

Applicant's or representative's reference

N400458EP-A

	Description of document	Original file name	Assigned file name
1	Request for extension of time limit during examination procedure	Request examination report extension - N400458EP-A DXP.PDF	EXRE92-1.PDF

	Payment	
1	Method of payment	Not specified

Signatures

Place: **London**
Date: **21 June 2021**
Signed by: **David Power 23473**
Association: **J A Kemp LLP**
Representative name: **/David POWER/**
Capacity: **(Representative)**

N400458EP-A



Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	9915801	
Application number	EP17168808.8	
Date of receipt	21 June 2021	
Receiving Office	European Patent Office, The Hague	
Your reference	N400458EP-A	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (1 p.)	ep-sfd-request.xml EXRE92-1.PDF\Request examination report extension - N400458EP-A DXP.PDF (1 p.)
Submitted by	CN=David Power 23473	
Method of submission	Online	
Date and time receipt generated	21 June 2021, 10:15 (CEST)	
Message Digest	71:81:EE:E0:5E:E1:B4:9F:B0:14:82:DE:E0:04:39:A4:15:8C:06:12	

/European Patent Office/



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp LLP
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
24.06.21

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1112 / 3222285
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Extension of time limit pursuant to Rule 132(2) EPC

Examination procedure

With reference to your request, the time limit for replying to the communication pursuant to Article 94(3) EPC dated 23.02.21 has been extended

by 2 months

to a total of 6 months

from the date of notification of the above-mentioned communication.

Please note: To the extent that your request exceeded the above extension, your request has been refused.

Note

The granting of extensions to time limits is governed by the Implementing Regulations to the EPC and the Guidelines for Examination in the EPO, E-VIII, 1.6. A request for extension, which would result in the total period set exceeding six months, must be reasoned and supported by evidence.

If no reply to the communication is received in due time, the European patent application will be deemed to be withdrawn (Art. 94(4) EPC).

Important information in case of a PACE request

If a PACE request has been validly filed for the application, the applicant is herewith informed that with the grant of the request for extension of time limit the application is removed from the PACE programme. A second PACE request for that application during the same stage of the procedure will not be processed (see OJ EPO 2015, A93, point 4).

For the Examining Division



Request for changes relating to an association of professional representatives

European Patent Office
Directorate 5.2.3 – Legal Division
80298 Munich
GERMANY

Name of association

J A Kemp LLP

Registration No.

811

Address

14 South Square
Gray's Inn
GB-LONDON WC1R 5JJ

I. Request for a change in the composition

We request registration of a change in the composition of the association with effect from the date of receipt of the present request at the EPO or from the following subsequent date

Date

Members to be added¹ (see additional sheet where necessary)

Surname	First name	Representative No.	Signature	Date

Members to be deleted¹ (see additional sheet where necessary)

Surname	First name	Representative No.	Signature	Date



Confirmation by at least one member of the association (see additional sheet where necessary)

Surname	First name	Representative No.	Signature	Date

¹ This form is only valid for changes relating to an association. If the address in the list of professional representatives before the European Patent Office (see Article 134(1) EPC) should also be changed, a separate request using EPO Form 52301 (Request for registration of changes relating to an entry in the list of professional representatives before the European Patent Office) should be filed.

II. Request for a change of name¹

We request registration of a change of name of the association with effect from the date of receipt of the present request at the EPO or from the following subsequent date

Date

The new name is

☒ Confirmation by at least one member of the association (see additional sheet where necessary)

Surname	First name	Representative No.	Signature	Date

III. Request for a change of address¹

☒ We request registration of a change of address of the association with effect from the date of receipt of the present request at the EPO or from the following subsequent date

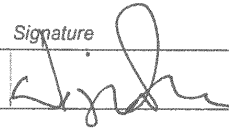
Date

27.9.21

The new address is

80 Turnmill Street
GB-LONDON EC1M 5QU

☒ Confirmation by at least one member of the association (see additional sheet where necessary)

Surname	First name	Representative No.	Signature	Date
Price	Nigel John King	62100		20.9.21

IV. Number of annexes (e.g. additional sheet for further members)

¹ This form is only valid for changes relating to an association. If the address in the list of professional representatives before the European Patent Office (see Article 134(1) EPC) should also be changed, a separate request using EPO Form 52301 (Request for registration of changes relating to an entry in the list of professional representatives before the European Patent Office) should be filed.



European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact



J A Kemp LLP
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Formalities officer
Ruiz Fernandez, José

Date
28-09-2021

Reference N400458EP-A	Application No./Patent No. 17168808.8 - 1112 / 3222285
Applicant/Proprietor Regeneron Pharmaceuticals, Inc.	

Noting of loss of rights pursuant to Rule 112(1) EPC

The European patent application is deemed to be withdrawn under Article 94(4) EPC, because the invitation to file observations on the communication from the Examining Division dated 23.02.21 was not complied with.

Means of redress

Request for a decision (R. 112(2) EPC)

If the applicant considers that the finding of the European Patent Office is inaccurate, he may, within a (non-extendable) period of **two months** after notification of this communication, apply in writing for a decision on the matter. The application can only lead to the finding being reversed if this does not actually correspond to the factual or legal situation.

Further processing (Art. 121 EPC)

The legal consequence of the failure to observe the time limit shall be deemed not to have ensued if, within a (non-extendable) period of **two months** after notification of this communication, further processing is requested by payment of the fee prescribed under Article 2(1)12 of the Rules relating to Fees and the omitted act is completed (R. 135(1) EPC).

Making payments

For payments made via deposit account, please note that as from 1 December 2017 debit orders will only be carried out if filed in an electronically processable format (xml), using an accepted means of filing as laid down in the Arrangements for deposit accounts (ADA), published in the Supplementary publication in the Official Journal.

All relevant information related to the modes of payment of fees to the EPO can be retrieved from the EPO website at **"Making Payments"**.

Information concerning fee amounts

Procedural fees are usually adjusted every two years, on even years, with effect from 1 April. Therefore, before making a payment, parties should verify the amounts actually due on the date of payment using the applicable version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, available on the EPO website (www.epo.org) at www.epo.org/schedule-of-fees. The "Schedule of fees" table allows the viewing, downloading and searching of individual fee amounts, both current and previous.

Date

Application No. 17168808.8

Important note to users of the automatic debiting procedure

The fee for further processing will be debited automatically on the day on which the above-mentioned omitted act is completed.

For the Examining Division

