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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 July 2007 (26.07.2007)

PCT

(10) International Publication Number
WO 2007/084765 A2

(51) International Patent Classification:
A61P 27/02 (2006.01) *A61K 39/395* (2006.01)
A61F 2/14 (2006.01) *A61K 38/17* (2006.01)
A61K 47/06 (2006.01) *A61K 31/00* (2006.01)

(21) International Application Number:
PCT/US2007/001649

(22) International Filing Date: 19 January 2007 (19.01.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/760,974 19 January 2006 (19.01.2006) US
11/544,389 6 October 2006 (06.10.2006) US

(71) Applicant *(for all designated States except US)*: **POTENTIA PHARMACEUTICALS, INC.** [US/US]; 201 East Jefferson Street, Suite 311, Louisville, KY 40202 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DESCHATELETS, Pascal** [US/US]; 11031 Indian Legends, #202, Lexington, KY 40241 (US). **OLSON, Paul** [US/US]; 645 South 3rd Street, Apt. 227-E, Louisville, KY 40202 (US).

(74) Agent: **JARRELL, Brenda, Herschbach;** Choate, Hall & Stewart, LLP, Two International Place, Boston, MA 021 10 (US).

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

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

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

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

WO 2007/084765 A2

(54) **Title:** INJECTABLE COMBINATION THERAPY FOR EYE DISORDERS

(57) **Abstract:** The present invention provides composition, methods, and articles of manufacture for treating an eye disorder, e.g., a disorder characterized by macular degeneration, choroidal neovascularization, or retinal neovascularization. One method of the invention comprises the step of: administering first and second therapeutic agents to the subject's eye in a single procedure, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is administered as a sustained release formulation of the second therapeutic agent. For example, the first and second therapeutic agents are administered by intravitreal injection. The first therapeutic agent may be dissolved in a liquid medium located in the syringe and the sustained formulation of the second therapeutic agent may comprise an ocular implant or plurality of particles located in the needle. The therapeutic agents may be selected from the group consisting of angiogenesis inhibors and complement inhibitors.

INJECTABLE COMBINATION THERAPY FOR EYE DISORDERS

Cross-Reference to Related Applications

[0001] This application claims priority to, and the benefit of, U.S. Provisional Patent Application No. 60/760,974, filed Jan. 19, 2006, and U.S.S.N. 11/544,389, filed Oct. 6, 2006, both of which are incorporated herein by reference.

Background of the Invention

[0002] Macular degeneration is a term that refers to and describes a number of different diseases characterized by degenerative changes in the macula, all of which lead to a loss of central vision. The macula is a small area in the retina of the eye, approximately 3 to 5 millimeters in size, adjacent to the optic nerve. It is the most sensitive area of the retina and contains the fovea, a depressed region that allows for high visual acuity and contains a dense concentration of cones, the photoreceptors that are responsible for color vision. Age-related macular degeneration (ARMD) is the most common cause of functional blindness in developed countries for those over 50 years of age. The disease is characterized by progressive degeneration of the retina, retinal pigment epithelium (RPE), and underlying choroid (the highly vascular tissue that lies beneath the RPE, between the retina and the sclera). Cells in the RPE recycle visual pigment (rhodopsin), phagocytose photoreceptor tips daily as part of rod and cone regeneration, and transport fluid across the membrane to the choroid. Central vision deteriorates when cells in the RPE cease to function properly. Despite extensive investigation, the pathogenesis of ARMD is not fully understood. Oxidative stress, inflammation, genetic background, and environmental or behavioral factors such as smoking and diet may contribute.

[0003] A clinical hallmark of ARMD is the appearance of drusen, localized deposits of lipoproteinaceous material that accumulate in the space between the RPE and Bruch's membrane. Drusen are typically the earliest clinical finding in ARMD, and the existence, location, and number of drusen are used in classifying the disease into stages and monitoring progression (Ambati, J., et al., *Surv. Ophthalmol.*, 48(3): 257-293, 2003; "Preferred Practice Pattern: Age-Related Macular Degeneration", American Academy of Ophthalmology, 2003).

[0004] ARMD has been classified into "dry" and "wet" (exudative, or neovascular) forms. Dry ARMD is much more common than wet, but the dry form can progress to the wet form, and the two occur simultaneously in a significant number of cases. Dry ARMD is typically characterized by progressive apoptosis of cells in the RPE, overlying photoreceptor cells, and frequently also the underlying cells in the choroidal capillary layer. Confluent areas (e.g., at

least 175 ∞m in minimum diameter) of RPE cell death accompanied by overlying photoreceptor atrophy are referred to as geographic atrophy. Patients with this form experience a slow and progressive deterioration in central vision. Wet ARMD is characterized by bleeding and/or leakage of fluid from abnormal vessels that have grown from the choroidal vessels (choriocapillaris) beneath the RPE and macula. This can be responsible for sudden and disabling vision loss. Much of the vision loss that patients experience is due to such choroidal neovascularization (CNV) and its complications. A subtype of neovascular ARMD in which angiomatous proliferation originates from the retina and extends posteriorly into the subretinal space, eventually communicating in some cases with choroidal new vessels has been identified (Yannuzzi, L.A., et al., *Retina,* 21(5):416-34, 2001). This form of neovascular ARMD, termed retinal angiomatous proliferation (RAP) can be particularly severe. The existence of macular drusen is a strong risk factor for development of both wet and dry forms of ARMD.

[0005] The panels of Figure 1 show structures present in a normal eye and some of the processes that occur in ARMD. Figures 1A and 1B show structures present in the anterior and posterior segments of the eye. Figures 1C-1E depict the outer layers of a normal eye (1C), an eye suffering from dry ARMD (1D), and an eye suffering from wet ARMD (1E). The outer nuclear layer (ONL) contains nuclei of rod and cone photoreceptors. Each photoreceptor contains an inner segment (IS) and outer segment (OS), the latter of which contains the pigment rhodopsin, which initiates the phototransduction cascade following exposure to light. The RPE lies below the photoreceptors and above Bruch's membrane. As shown in Figures 1D and 1E, the normal structure of the retina is disrupted in a variety of ways as in patients with ARMD.

[0006] Macular edema is associated with a variety of eye disorders including ARMD, diabetic retinopathy, inflammatory conditions such as anterior or posterior uveitis, etc. The macula becomes thickened as a result of the accumulation of fluid that leaks from weakened or otherwise abnormal blood vessels into nearby tissues. Leakage of blood or other fluids and the resulting increase in macular thickness can lead to acute alterations in visual acuity, color perception, etc. Thus macular edema can contribute to the visual disturbances and loss experienced by individuals suffering from ARMD and a variety of other eye disorders.

[0007] Development of pharmacological therapies for ARMD and other ocular disorders associated with neovascularization in the eye is an area of active investigation. Much effort has focused on methods for destroying or sealing abnormal blood vessels and/or inhibiting their development. Photodynamic therapy involves systemic intravenous administration of a light-sensitive dye (verteporfin) which is activated in the eye by a laser, resulting in formation of toxic products within the abnormal blood vessels. Local administration of angiogenesis inhibitors to

the eye shows considerable promise. Pegaptanib sodium (Macugen®; Pfizer/Eyetech) was approved by the U.S. Food and Drug Administration for treatment of wet age-related macular degeneration in late 2004. Macugen is an aptamer that binds to an isoform of vascular endothelial growth factor (VEGF), a protein that acts as a signal in triggering the abnormal blood vessel growth, increased permeability, and consequent leakage that characterize wet ARMD. Binding of Macugen to VEGF prevents it from binding to VEGF receptors, thereby inhibiting its activity. Other angiogenesis inhibitors for the treatment of exudative ARMD include monoclonal antibodies such as ranibizumab (Lucentis®; Genentech) that bind to VEGF and block its interaction with VEGF receptors.

[0008] Angiogenesis inhibitors that interfere with signal transduction pathways that play a fundamental role in angiogenesis, such as the VEGF pathway, offer a powerful approach to controlling neovascularization. However, therapy with angiogenesis inhibitors alone has a number of disadvantages. Clinical trials of angiogenesis inhibitors that interfere with the VEGF pathway have involved their administration in solution by intravitreal injection at intervals of 4-6 weeks. Unfortunately this procedure is associated with a significant risk of complications such as traumatic lens injury, retinal detachment, and endophalmitis associated with either trauma or intraocular infection. With an overall risk of 1%, over the course of a year a dosing interval of 6 weeks would result in an overall risk of about 9% per eye, while a dosing interval of 4 weeks would result in an overall risk of about 13% per eye. For these and other reasons, current approaches to the use of angiogenesis inhibitors remain a less than optimal solution to treating wet ARMD. There remains a need in the art for improved approaches to treating ARMD. There also remains a need for improved approaches to treating other conditions characterized by macular degeneration, choroidal neovascularization, retinal neovascularization, retinal angiomatous proliferation, and/or blood vessel leakage in the eye.

Summary of the Invention

[0009] The present invention provides compositions, methods, and articles of manufacture for the treatment of eye disorders, particularly those associated with macular degeneration, CNV, and/or retinal neovascularization (RNV). In one aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV_5 or RNV, the method comprising the step of: administering first and second therapeutic agents to the subject's eye in a single procedure, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is administered as a sustained

release formulation of the second therapeutic agent. In certain embodiments of the invention the second therapeutic agent is a long-acting therapeutic agent. In certain embodiments of the invention at least a portion of the first therapeutic agent, optionally essentially the entire administered dose of the first therapeutic agent, is provided as a component of a sustained release formulation. The first and second therapeutic agents may be provided as components of a single sustained release formulation or as components of separate sustained release formulations.

[OOIOJ In certain embodiments of the invention the procedure is an injection procedure, e.g., an intravitreal injection. In certain embodiments the procedure is an injection procedure in which, prior to administration, the first therapeutic agent is contained in a syringe and the sustained release formulation comprising the second therapeutic agent is contained in a needle attached to the syringe. For example, the first therapeutic agent may be dissolved in a liquid medium located in the syringe and the sustained formulation of the second therapeutic agent may comprise an ocular implant located in the needle.

[0011] In another aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV comprising the step of: administering first and second compositions to a subject's eye in a single procedure, wherein the first composition comprises a first therapeutic agent that provides rapid improvement in the condition of the subject's eye and the second composition comprises a second therapeutic agent that is administered as a sustained release formulation comprising the second therapeutic agent. Either or both of the compositions can contain a plurality of therapeutic agents, e.g., two or more angiogenesis inhibitors, two or more complement inhibitors, or an angiogenesis inhibitor and a complement inhibitor.

[0012] In another aspect the invention provides a method of administering first and second therapeutic agents to the eye of a subject comprising: injecting (i) a solution containing the first therapeutic agent and (ii) a solid ocular implant containing the second therapeutic agent into the subject's eye in a single injection procedure.

[0013] In any embodiment of the invention, either or both therapeutic agents may be an angiogenesis inhibitor or a complement inhibitor. In any embodiment of the invention the sustained release formulation may comprise an ocular implant. In any embodiment of the invention the sustained release formulation may comprise a polymer and one or more therapeutic agents.

[0014] In other aspects, the invention provides articles of manufacture. The invention provides an article of manufacture comprising (i) a first therapeutic agent effective for treating

DOCKET ALARM

Explore Litigation Insights

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

Real-Time Litigation Alerts

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

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

Advanced Docket Research

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

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

Analytics At Your Fingertips

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

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

API

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

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

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

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.